Table A.43 Withdrawal-Lack of Arthritis Efficacy (Protocols 022, 023)

Text Table 40. Reasons for Study Termination (All Randomized Patients: 12-Week Pivotal Studies 022 and 023 and 12-Week Pooled Pivotal Studies)

	Number of Rheumatoid Arthritis Patients by Treatment Group				
		Celecoxib			Naproxen
Study	Placebo	100 mg BID	200 mg BID	400 mg BID	500 mg BID
Study 022	**(n=231)**	**(n=240)**	**(n=235)**	**(n=218)[a]**	**(n=225)**
Total Completed	**101 (44%)**	**154 (64%)**	**158 (67%)**	**137 (63%)**	**138 (61%)**
Total Withdrawn	**130 (56%)**	**86 (36%)**	**77 (33%)**	**81 (37%)**	**87 (39%)**
Lost to Follow-up	3 (1%)	1 (<1%)	3 (1%)	1 (<1%)	1 (<1%)
Pre-Existing Violation	2 (<1%)	1 (<1%)	3 (1%)	2 (<1%)	0 (0%)
Protocol Non-Compliance	10 (4%)	4 (2%)	4 (2%)	7 (3%)	9 (4%)
Treatment Failure	104 (45%)	67 (28%)	50 (21%)	59 (27%)	65 (29%)
Adverse Event	11 (5%)	13 (5%)	17 (7%)	12 (6%)	12 (5%)
Study 023	**(n=221)**	**(n=228)**	**(n=219)[a]**	**(n=217)**	**(n=218)**
Total Completed	**78(35%)**	**117 (51%)**	**124 (57%)**	**126 (58%)**	**133(61%)**
Total Withdrawn	**143 (65%)**	**111 (49%)**	**95 (43%)**	**91 (42%)**	**85(39%)**
Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)	2 (<1%)	0 (0%)
Pre-Existing Violation	2(<1%)	2 (<1%)	3 (1%)	2 (<1%)	0 (0%)
Protocol Non-Compliance	4 (2%)	5 (2%)	2 (<1%)	2 (<1%)	0 (0%)
Treatment Failure	125 (57%)	92 (40%)	74 (34%)	69 (32%)	69(32%)
Adverse Event	12 (5%)	12 (5%)	16 (7%)	16 (7%)	16 (7%)
Pooled[b]	**(n=452)**	**(n=468)**	**(n=454)[a]**	**(n=435)[a]**	**(n=443)**
Total Completed	**179 (40%)**	**271 (58%)**	**282 (62%)**	**263 (60%)**	**271 (61%)**
Total Withdrawn	**273 (60%)**	**197 (42%)**	**172 (38%)**	**172 (40%)**	**172 (39%)**
Lost to Follow-up	3 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)	1 (<1%)
Pre-Existing Violation	4 (<1%)	3 (<1%)	6 (1%)	4 (<1%)	0 (0%)
Protocol Non-Compliance	14 (3%)	9 (2%)	6 (1%)	9 (2%)	9 (2%)
Treatment Failure	229 (51%)	159(34%)	124 (27%)	128 (29%)	134 (30%)
Adverse Event	23 (5%)	25 (5%)	33 (7%)	28 (6%)	28 (6%)

Derived from Individual Study Reports

a) Total number of patients includes two patients (one in the celecoxib 200 mg BID group [Study 023] and one in the celecoxib 400 mg BID group [Study 022]) who were randomized but did not receive study medication and are not included in the ITT Cohort.

b) Pooled represents data from combined pivotal Studies 022 and 023.

Table A.44 Time to Withdrawal - Lack of Arthritis Efficacy (023)

[redacted] COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN RA
[redacted]

TABLE 28
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 1 OF 2: KAPLAN-MEIER ESTIMATES OF PROPORTION OF PATIENTS WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)

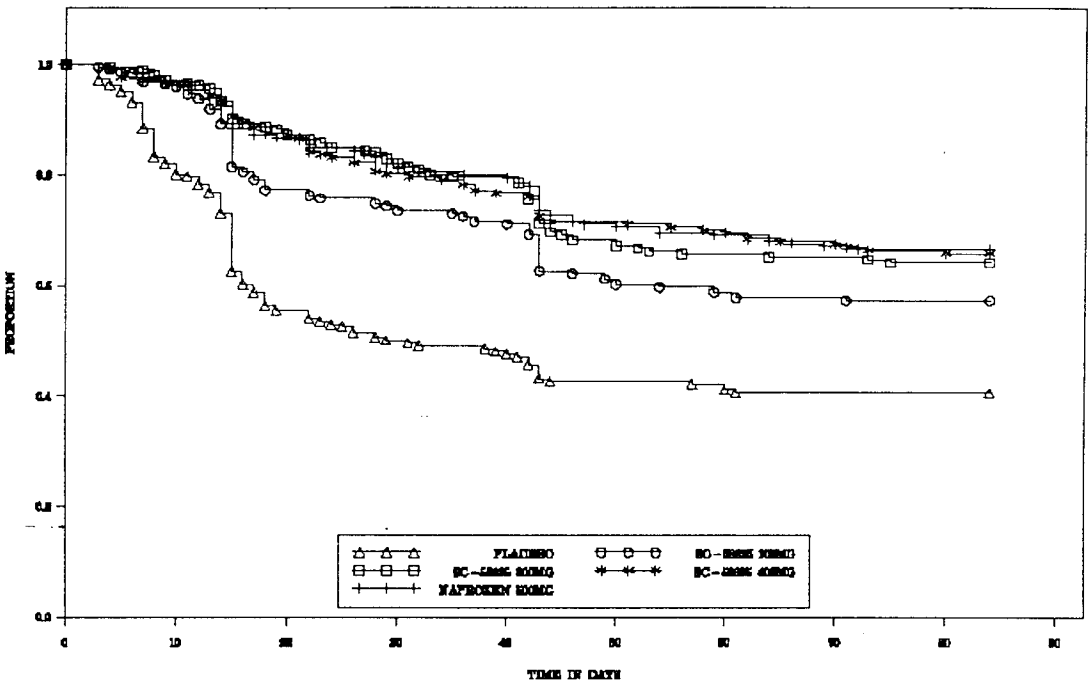


TABLE 28
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 2 OF 2: LOG-RANK TESTS FOR TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)

p-VALUES FOR OVERALL COMPARISONS (a): <0.001

p-VALUES FOR TREATMENT COMPARISONS (b):

100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
<0.001	<0.001	<0.001	0.092	0.049	0.774	<0.001	0.035	0.647	0.878

(a) From log-rank test for all five treatment groups
(b) From pairwise log-rank test

Table A.45 Summary of Dosage change-OA /RA(protocol 024)

Table 9.7
Summary of Dosage Change - Long Term Open Label Trial

024 Starting Dose	OA Withdrawals (N = 659)	OA Still Active (N = 1895)	OA Combined (N = 2554)
Celecoxib 100 mg BID			
NO CHANGES	193(29.3%)	469(24.7%)	662(25.9%)
INCREASE IN DOSE	444(67.4%)	1372(72.2%)	1816(71.1%)
100-200	437(66.3%)	1369(72.2%)	1806(70.7%)
100-300	3(0.5%)	1(< 0.1%)	4(0.2%)
100-400	2(0.3%)	0(0.0%)	2(< 0.1%)
OTHER	2(0.3%)	0(0.0%)	2(< 0.1%)
MULTIPLE CHANGES	22(3.3%)	56(3.0%)	78(3.1%)
100-200-100	13(2.0%)	26(1.4%)	39(1.5%)
100-200-100-200	4(0.6%)	21(1.1%)	25(1.0%)
100-200-100-200-100	1(0.2%)	0(0.0%)	1(< 0.1%)
100-200-100-other-200	0(0.0%)	1(< 0.1%)	1(< 0.1%)
100-200-300-200	1(0.2%)	2(0.1%)	3(0.1%)
100-200-300-other-200	0(0.0%)	1(< 0.1%)	1(< 0.1%)
100-200-other	1(0.2%)	1(< 0.1%)	2(< 0.1%)
100-200-other-100-200	1(0.2%)	0(0.0%)	1(< 0.1%)
100-200-other-200	0(0.0%)	1(< 0.1%)	1(< 0.1%)
100-300-200	0(0.0%)	1(< 0.1%)	1(< 0.1%)
100-other-200	1(0.2%)	2(0.1%)	3(0.1%)

'Other' means celecoxib doses of 300 mg AM/200 mg PM, 200 mg AM/100 mg PM, 400 mg AM/300 mg PM, 100 mg QD, or 100 mg TID.

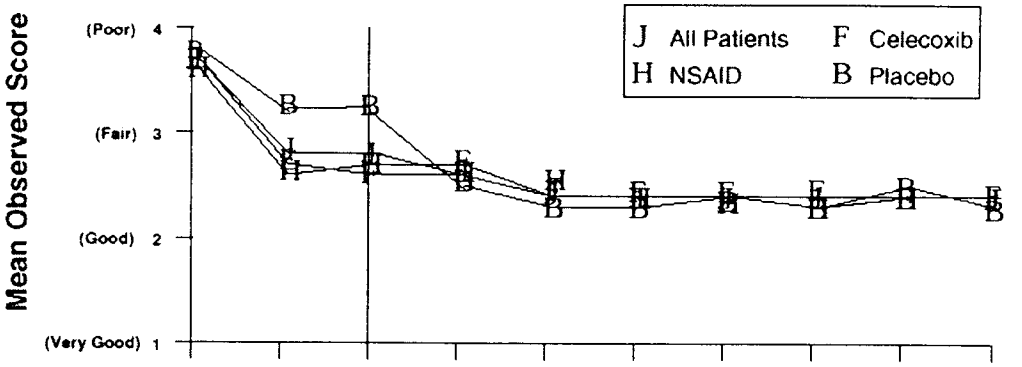
Table 9.7
Summary of Dosage Change - Long Term Open Label Trial

024 Start Dose	RA Withdrawals (N = 523)	RA Still Active (N = 1422)	RA Combined (N = 1945)
Celecoxib 200 mg BID			
NO CHANGES	121(23.1%)	315(22.2%)	436(22.4%)
INCREASE IN DOSE	368(70.4%)	1023(71.9%)	1391(71.5%)
200-300	117(22.4%)	374(26.3%)	491(25.2%)
200-400	251(48.0%)	648(45.6%)	899(46.2%)
OTHER	0(0.0%)	1(< 0.1%)	1(< 0.1%)
DECREASE IN DOSE	4(0.8%)	5(0.4%)	9(0.5%)
MULTIPLE CHANGES	30(5.7%)	79(5.6%)	109(5.6%)
200-100-200	3(0.6%)	4(0.3%)	7(0.4%)
200-100-200-100	1(0.2%)	0(0.0%)	1(< 0.1%)
200-100-200-300	0(0.0%)	1(< 0.1%)	1(< 0.1%)
200-100-200-300-400	2(0.4%)	1(< 0.1%)	3(0.2%)
200-100-200-400	1(0.2%)	0(0.0%)	1(< 0.1%)
200-100-300-400-200	1(0.2%)	0(0.0%)	1(< 0.1%)
200-100-400-200	1(0.2%)	0(0.0%)	1(< 0.1%)
2[illegible]-100-200-100	0(0.0%)	1(< 0.1%)	1(< 0.1%)
[illegible]-400-300	0(0.0%)	1(< 0.1%)	1(< 0.1%)
[illegible]-100	0(0.0%)	1(< 0.1%)	1(< 0.1%)
[illegible]-200	7(1.3%)	19(1.3%)	26(1.3%)
[illegible]-200-400	0(0.0%)	5(0.4%)	5(0.3%)
200-300-200-300-200	0(0.0%)	2(0.1%)	2(0.1%)
200-300-200-300-400	0(0.0%)	3(0.2%)	3(0.2%)
[illegible]-400-300-400-200	0(0.0%)	1(< 0.1%)	1(< 0.1%)
200-300-400-100-200-300-400	1(0.2%)	0(0.0%)	1(< 0.1%)
200-300-400-200	2(0.4%)	3(0.2%)	5(0.3%)
200-300-400-200-200	0(0.0%)	1(< 0.1%)	1(< 0.1%)
200-300-400-200-300-400	0(0.0%)	1(< 0.1%)	1(< 0.1%)
200-300-400-200-400	0(0.0%)	2(0.1%)	2(0.1%)
200-300-400-200-other-100-other-200-300	1(0.2%)	0(0.0%)	1(< 0.1%)
200-300-400-300	7(1.3%)	11(0.8%)	18(0.9%)

'Other' means celecoxib doses of 300 mg AM/200 mg PM, 200 mg AM/100 mg PM, 400 mg AM/300 mg PM, 100 mg QD, or 100 mg TID.

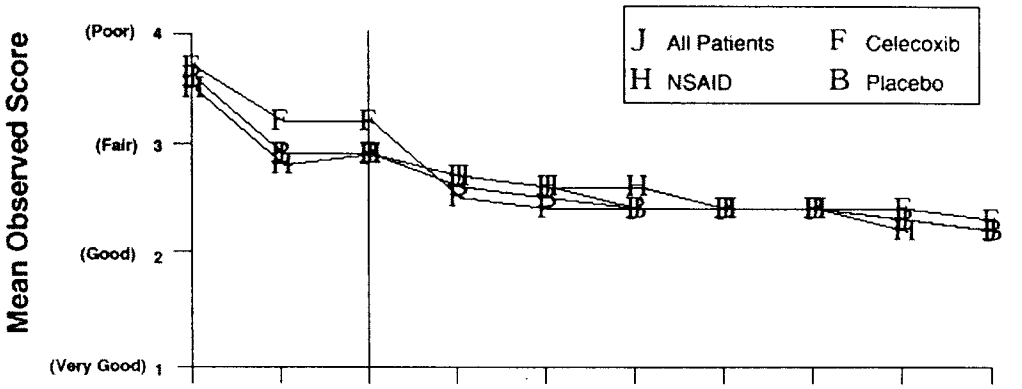
Figure A.1 Patient's Global Assessment-OA/RA (protocol 024)

Figure 7. **Patient's Global Assessment of Arthritic Condition: OA Patients (Study 024)**



All 2554	2554	2549	2453	2109	1602	990	665	270	84
Celecoxib 1579	1579	1578	1534	1341	1017	629	433	179	67
NSAID 503	502	501	459	349	247	153	89	26	0
Placebo 472	472	470	460	419	338	208	143	65	17

Figure 10. **Patient's Global Assessment of Arthritic Condition: RA Patients (Study 024)**



All 1945	1945	1943	1865	1669	1439	1089	722	294	111
Celecoxib 1197	1197	1197	1155	1039	890	672	455	193	78
NSAID 360	360	360	331	280	235	163	99	18	0
Placebo 388	388	386	379	350	314	254	168	83	33

Management of Pain Indication for Celecoxib – A Brief Medical Review Summary

For the "general purpose" management of acute pain the usual requirement is (replicated) evidence of efficacy in at least two different type of pain models. One of which should be a model using multiple doses over several days in patients requiring short-term therapy.

During the development program of celecoxib, six studies were conducted to support the management of pain indication. Four single dose studies in the dental pain model (025, 027, 070, 005) and two multiple dose studies in the post orthopedic/general surgery model (028, 029,).

Of the four dental pain studies, three are considered to be pivotal (study 005 had a single blind design). In these studies, celecoxib at doses of 100 mg SD (Studies 027 and 070), 200 mg SD (Studies 025, 027 and 070), and 400 mg SD (Study 070) showed statistically significantly greater improvement in pain compared to placebo beginning at 1 hour postdose and continuing through nearly 8 hours postdose for the time specific efficacy measures. Time to Rescue Medication was statistically significant longer compared to placebo with celecoxib doses of 50 mg, 100 mg, 200 mg and 400 mg. Shorter Time to Perceptible Pain Relief compared to placebo was statistically significant for only the 200 mg dose (Studies 025 and 027). It is important to note that the NSAID comparators (ibuprofen 400mg and naproxen sodium 550mg) demonstrated a more rapid onset of analgesia and a statistically significantly greater peak response than celecoxib at all doses studied (25 mg, 50 mg , 100 mg, 200 mg, and 400 mg).

In the two multiple dose post general/orthopedic surgical pain studies interim analyses (not included in the protocol) were conducted. The reason given was that: "the enrollment had been slower than expected and the dropout rate had been higher than expected, raising concerns that the model was not behaving as anticipated". Study 029 (post general surgery) was terminated because neither celecoxib nor the comparator (Darvocet-N) separated statistically from placebo. In the multiple dose post-orthopedic surgery trial (028) the only statistically significant differences favoring celecoxib over the placebo were at a dose of 200 mg for the pain relief plus pain intensity difference (PRID) measurement, at 6, 7, and 9 hours. Therefore, no substantial evidence has been demonstrated in the multiple dose post general/orthopedic surgical pain studies to support the management of pain indication.

Conclusions

A key issue here is whether a new molecular entity can gain a management of pain indication based only on evidence from single dose studies in one type of pain model. Although the results of the osteoarthritis studies lend some general support to idea that celecoxib can have an analgesic effect, the evidence of its utility for acute analgesic is weak; it "won" in three pivotal, single dose dental pain studies, but it appeared to be less effective than ibuprofen or naproxen sodium; and celecoxib failed in showing statistically

significant efficacy in the treatment of pain in two multiple dose, 3-5 day post operative trials.

Recommendations

1. This drug is recommended not approval for the treatment of pain at this time.
2. If additional multiple dose, 3-5 day studies show a statistically significant efficacy in the treatment of acute pain, the results of the currently submitted studies might serve as a supportive evidence.
3. If and when this drug is approved for the treatment of pain it is recommended that the labeling will reflect its performance relative to other NSAID's.

DRAFT

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

MEDICAL OFFICER REVIEW
ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG
PRODUCTS DIVISION—HFD-550

NDA #:	**20,998**
SUBMISSION DATE:	July 8, 1998
REVIEWER:	Mordechai Averbuch, MD
PRODUCT:	**CELEBREX® (Celecoxib)**
REVIEW DATE:	October 22, 1998
SPONSOR:	G.D. Searle & Co. 4901 Searle Parkway Skokie, Illinois 60077 Phone (847) 982-7000
PHARMACOLOGICAL CATEGORY:	COX 2 Selective Inhibitor, Anti-inflammatory
PROPOSED INDICATIONS:	1) Acute or chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis. 2) Management of pain.
DOSAGE FORM & ROUTE:	Oral capsules, 100mg and 200mg
CSO:	V. Lutwak

ATTENTION:

This review is for the section of this NDA submitted to support the indication of the management of pain only. Studies supporting the indication of acute or chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis, as well as other clinical studied conducted to support the safety profile of celecoxib, are being reviewed by other medical reviewers.

RESUME:

Six clinical trials have been conducted to support the management of pain indication.
Four single dose, post third molar extraction studies, three of them are considered to be pivotal.
Two multiple dose, 3-5 day, post general and orthopedic surgery studies, one of them is considered to be pivotal.

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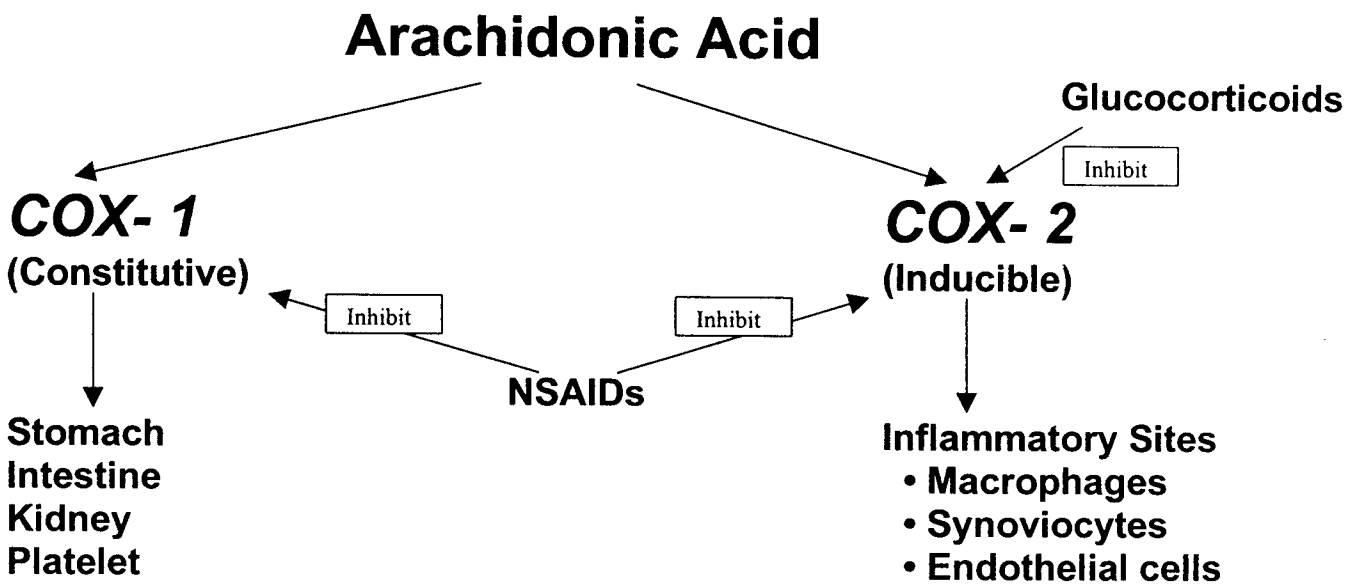
DRAFT

Listing of Tables

INTRODUCTION:

Currently, the class of agents most commonly used for anti-inflammatory and analgesic conditions is the nonsteroidal anti-inflammatory drugs (NSAIDs). Although the mechanism by which NSAIDs achieve their effect is not completely understood, they are known to inhibit the activity of the enzyme cyclooxygenase (COX), which mediates conversion of arachidonic acid to the prostaglandins that serve as key components of inflammatory processes. However, prostaglandins are also needed to maintain normal gastrointestinal and platelet function, as well as renal function under physiologically stressed conditions. Thus, the anti-inflammatory and analgesic benefits of NSAID therapy are tempered by an increased risk of gastrointestinal ulceration and ulcer complications (such as bleeding, perforation, and gastric outlet obstruction), hemorrhagic diathesis, and nephrotoxicity. Recently, two distinct isoforms of COX were identified and designated COX-1 and COX-2. COX-1 is constitutively expressed in most tissues throughout the body, including the gastrointestinal tract, kidney, and platelets. COX-2, a cytokine-inducible enzyme, is normally found in very low amounts in healthy tissue (except the brain and kidney) but is prominently expressed in inflamed tissues. It is particularly noteworthy that COX-2 is not expressed in platelets or the gut. Studies of recombinant enzymes in vitro and in cell lines have demonstrated that as a class, NSAIDs nonselectively inhibit the activity of both COX-1 and COX-2 (figure).

Figure: Roles of COX-1 and COX-2 in Physiologic and Pathophysiologic Functions.



These findings gave rise to the hypothesis that the gastrointestinal, platelet, and renal toxicity of NSAIDs results from inhibition of COX-1, while their therapeutic benefit is a function of inhibition of COX-2. Evidence supporting this hypothesis has been provided by studies showing that:

- COX-2 expression is up-regulated by inflammatory mediators such as cytokines and bacterial endotoxin;
- up-regulation of COX-2 expression is blocked by anti-inflammatory glucocorticoids, which do not alter COX-1 expression; and
- in animals, selective inhibition of COX-2 is anti-inflammatory and analgesic, but cause less gastroduodenal toxicity.

In contrast, NSAIDs, which nonselectively inhibit both COX-1 and COX-2, cause pronounced gastrointestinal toxicity and interfere with platelet function at therapeutic doses.

Celecoxib is a novel compound that selectively inhibits cyclooxygenase 2 and is being developed as an oral anti-inflammatory and analgesic agent seeking the indications of: the treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), and for the management of pain.

Summary of Clinical Studies Conducted in Patients with Postsurgical Pain

Six studies were conducted in patients with postsurgical pain, four in the dental pain model (025, 027, 070, 005) and two in the post orthopedic/general surgery model (028, 029,). Four of these studies are considered to be pivotal. However, only three of these studies (025, 027, and 070, all dental pain studies) provide substantial evidence of efficacy.

Studies 028 and 029 were multiple dose post general/orthopedic surgical pain studies. During the course of these trials, interim analyses (not included in the protocol) were conducted by an independent Data Monitoring Committee (DMC). The reason given was that: "the enrollment had been slower than expected and the dropout rate had been higher than expected, raising concerns that the model was not behaving as anticipated". The DMC recommended that Study 028 be continued. They recommended that Study 029 be terminated because the active comparator (Darvocet-N) did not separate statistically from placebo; placebo response was unexpectedly high. Study 029 was terminated, at which time approximately 70% of the patients had been enrolled. Therefore the study results are not discussed in detail in this summary. However, the data is presented in the individual study review.

A seventh study (Study 080) enrolled only one patient when a decision was made to discontinue the study. The reason given was that the comparator selected (naproxen) was not considered to be suitable for that pain model, and is not included in the ISE.

A summary of these studies is provided in tables 1 and 2.

Summary of Clinical Studies Conducted in Patients with Postsurgical Pain:

Table 1: Post Oral Surgery - Single Dose

Protocol No. Report No. Short Title	Study Design	Treatment Regimen(s)	Results (Efficacy)
P: N49-96-02-025 R: N49-97-16-025 Dose-ranging Analgesic Efficacy in Postsurgical Dental Pain	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Paralliel Group (single dose) ≥ 2 third molars	**Celecoxib** 25 mg (N=50), 50 mg (N=50), or 200 mg (N=50) **Ibuprofen** 400 mg (N=50) **Placebo** (N=50) Total N=250	Celecox.> Placebo Ibuprofen > Celecox.
P: N49-97-02-027 R: N49-97-06-027 Analgesic Efficacy in Postsurgical Dental Pain	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose) ≥ 2 third molars	**Celecoxib** 100 mg (N=55) or 200 mg (N=56) **Naproxen Sodium** 550 mg(N=54) **Placebo** (N=55) Total N=220	Celecox.> Placebo Naproxen > Celecox.
P: N49-97-02-070 R: N49-97-06-070 Dose-response and Analgesic Efficacy in Postsurgical Dental Pain	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (single dose) ≥ 1 third molars	**Celecoxib** 50 mg (N=35), 100 mg (N=50), 200 mg (N=50), or 400 mg (N=35) **Naproxen Sodium** 550 mg (N=35) **Placebo** (N=50) Total N=225	Celecox.> Placebo Naproxen > Celecox.
P: N49-95-02-005 R: N49-97-16-005 Analgesic Efficacy in Postsurgical Dental Pain	Randomized, *Single-Blind*, Placebo-Controlled, Active Controlled, Parallel Group (single dose) > 1 third molars	**Celecoxib** 100 mg (N=50) or 400 mg (N=50) **Aspirin** 650 mg (N=50) **Placebo** (N=50) Total N=200	Celecox.> Placebo Aspirin = Celecox.

Table 2: Post General and Orthopedic Surgery

Protocol No. Report No. Short Title	Study Design (Duration of Treatment)	Treatment Regimen(s)	Results (Efficacy)
P: N49-96-02-028 R: N49-98-06-028 Multiple-dose Analgesic Efficacy after Orthopedic Surgery	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (5 days)	**Celecoxib** 100 mg PRN up to BID or 200 mg PRN up to BID **Darvocet-N®** 100 mg PRN up to QID **Placebo**	No superiority of neither drug over placebo **Interim analysis performed**
P: N49-96-02-029 R: N49-98-06-029 Multiple-dose Analgesic Efficacy after General (but not Orthopedic) Surgery	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Parallel Group (5 days)	**Celecoxib** 100 mg PRN up to BID or 200 mg PRN up to BID **Darvocet-N®** 100 mg PRN up to QID or **Placebo**	N/A **Terminated after interim analysis**
P: N49-97-02-080* R: N49-98-06-080 Multiple-dose Analgesic Efficacy after Orthopedic Surgery	Randomized, Double-Blind, Placebo-Controlled, Active-Controlled, Parallel Group (5 days)	**Celecoxib** 200 mg PRN up to BID **Naproxen** 500 PRN up to BID or Placebo	N/A **Stoped after enrolment of the first patient**

* Only one patient (naproxen 500 mg BID PRN group) was enrolled before this study was terminated. This study is not discussed in this ISE.

Studies Population and Design

Study Population and Design - Post-Oral Surgery
(Studies # 025, 027 and 070)

In order to be entered into the post-oral surgery pain studies, patients had to have undergone surgical extraction of one or more impacted third molar(s) requiring bone removal, one of which must have been mandibular, and been experiencing moderate to severe postsurgical pain, and rated their Baseline pain intensity ≥50 mm on a Visual Analog Scale (VAS) of 100 mm.

Studies 025, 027 and 070 were double blind, randomized, placebo-controlled, single-dose studies that contained an active control. These studies were comprised of a Pretreatment Visit, Surgical Procedure, a Baseline Visit, a 24-hour Treatment Period, and a Posttreatment Period. In these studies, the Pretreatment Visit occurred within 14 days prior to the administration of study medication. Each patient provided a medical history, underwent a limited physical examination, and had clinical laboratory tests performed. At the Surgical Procedure, the molar(s) was extracted and a surgical trauma rating was made by the oral surgeon. At the Baseline assessment, only patients experiencing moderate to severe pain within six hours of the completion of surgery were enrolled into the study.

The Treatment Period was the 24-hour period immediately following the administration of a single dose of study medication. Patients remained in the research unit for the 24-hour Treatment Period and underwent the scheduled pain assessments at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours postdose. Assessments included Pain Intensity (Categorical Scale), Pain Relief, Pain at Least Half Gone, Pain Intensity (VAS), Patient's Global Evaluation, and patients were provided two stopwatches with which to separately record Time to Perceptible and Meaningful Pain Relief. The use of potentially confounding medications in the postsurgical period was restricted as specified in the protocol. Patients were allowed to take rescue medication at any time in the study, if needed. Prior to taking the rescue medication the patients completed a final pain assessment and were then dropped from the study. For those patients who did not take rescue medication, the final pain assessments and end-of-study safety assessments were performed in the Posttreatment Period.

The design of Study 005 differed from Studies 025, 027, and 070 in that it was single blind, the study duration was 8 hours and stopwatches were not used. This study was not considered to be pivotal.

Study Population and Design - Post-Orthopedic and General Surgery Studies
(Studies # 028 & 029)

In order to be entered into either a post-orthopedic or post-general surgery study, patients had to have undergone an orthopedic procedure requiring open manipulation of bone with periosteal elevation (Study # 028) or a general surgical procedure (Study # 029) that was

expected to require administration of analgesics for management of pain for 3-5 days. Patients were to have received administration of the first dose of study medication within 54 hours after the end of anesthesia. The Baseline pain intensity (Categorical) must have been moderate to severe. Studies 028 and 029 were double-blind, randomized, placebo-controlled, multiple dose studies which contained an active control. Patients were allowed to receive analgesic medications such as Patient Controlled Analgesia (PCA) in the postsurgical period prior to first dose of study medication. If they were administered PCA during the postsurgical period, they must have tolerated and received pain relief from an oral analgesic medication prior to receiving study medication.

The post-general and orthopedic surgery studies were comprised of a Pretreatment Period which included the Screening Visit, Surgery, and the Baseline assessment. The Screening Visit occurred up to 14 days prior to surgery. Each patient gave a medical history, underwent a physical examination, and had clinical laboratory tests performed.

The Baseline assessment occurred within 54 hours after the end of anesthesia. The clinical laboratory tests performed at Screening were repeated. Immediately prior to study drug administration, each patient was asked to record the severity of his or her starting pain and only patients indicating moderate or severe pain were enrolled in the study.

The Treatment Period was defined as up to a five-day period after the first dose of study medication. Day 1 was defined as the 24-hour period beginning with the date and time of the first dose of study medication. Patients received the second dose of study medication not less than four hours after the first dose of study medication. Subsequent doses of study medication were administered as needed, no closer than two hours apart, and could not exceed four doses in 24 hours. In the celecoxib groups, only the first two doses were active, doses 3 and 4 were matching placebo. In contrast, all four doses of Darvocet-N 50 (2 tablets) were active. Patients received study medication and remained in the study for up to a maximum of 5 days. Patients underwent the following assessments at 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, and 24 hours postdose: Pain Intensity (Categorical Scale), Pain Relief, Pain at Least Half Gone, Pain Intensity (VAS), and were provided with a stopwatch to record Meaningful Pain Relief. In addition, the APS Pain Measure was completed by each patient every 24 hours after the first dose of study medication.

Final pain assessments were performed at the last hourly observation; just prior to rescue analgesia or just prior to hospital discharge.

Patient Disposition and Characteristics in Postsurgical Patients

A total of 1347 patients with postsurgical pain were enrolled into clinical studies with celecoxib. In the four post-oral surgery studies (Studies 025, 027, 070, 005), patients were randomized to receive one of nine treatments: celecoxib 25 mg single-dose (SD), celecoxib 50 mg SD, celecoxib 100 mg SD, celecoxib 200 mg SD, celecoxib 400 mg SD, naproxen sodium 550 mg SD, ibuprofen 400 mg SD, ASA 650 mg SD, or placebo (table 3).

Table 3: Number of Patients Listed by Study and Treatment Group – Dental Pain Studies (ITT Cohort: Studies 025, 027, 070, 005)

	Number of Postsurgical Patients by Treatment Group									
		Celecoxib					Naproxen Sodium	Ibuprofen	Aspirin	
Study Number	Placebo	25 mg SD	50 mg SD	100 mg SD	200 mg SD	400 mg SD	550 mg SD	400 mg SD	650 mg SD	Total
025	50	50	50	--	50	--	--	50	--	250
027	55	--	--	55	56	--	54	--	--	220
070	50	--	35	50	50	35	35	--	--	255
005	50	--	--	50	--	50	--	--	50	200
Total # of Patients	205	50	85	155	156	85	89	50	50	925

In the post-general and post-orthopedic surgery studies (Studies 028, 029), patients were randomized to receive one of four treatments: celecoxib 100 mg BID PRN, celecoxib 200 mg BID PRN, Darvocet-N 100 mg QID PRN or placebo (table 4).

Table 4: Number of Patients Listed by Study and Treatment Group (ITT Cohort: Studies 028, 029)

Study Number	Placebo	Celecoxib		Darvocet-N 100 mg QID PRN	Total
		100 mg BID PRN	200 mg BID PRN		
028	60	68	62	65	255
029	40	45	42	40	167
Total # Patients	100	113	104	105	422

Of the 925 randomized patients from the post-oral surgery studies, 225 (24%) completed the study and did not require additional analgesic medications during the study. Table 5 presents a summary of all patients, by treatment group, who completed each study. The reasons for study termination, grouped by treatment, for all randomized patients are also summarized in this table.

Table 5: Reasons for Study Termination (ITT Cohort: Studies 025, 027, 070, 005)

Study	Number of Postsurgical (Dental) Patients by Treatment Group							
		Celecoxib					Naproxen Sodium	Ibuprofen
	Placebo	25 mg SD	50 mg SD	100 mg SD	200 mg SD	400 mg SD	550 mg SD	400 mg SD
Study 025								
Total Completed [a]	4 (8%)	4 (8%)	7 (14%)	---	13 (26%)	---	---	8 (16%)
Total Withdrawn	46 (92%)	46 (92%)	43 (86%)	---	37 (74%)	---	---	42 (84%)
Treatment Failure/ Rescue Medication	46 (92%)	46 (92%)	43 (86%)	---	37 (74%)	---	---	42 (84%)
Adverse Event	0 (0%)	0 (0%)	0 (0%)	---	0 (0%)	---	---	0 (0%)
Study 027								
Total Completed [a]	9 (16%)	---	---	17 (31%)	27 (48%)	---	28 (52%)	---
Total Withdrawn	46 (84%)	---	---	38 (69%)	29 (52%)	---	26 (48%)[b]	---
Treatment Failure/ Rescue Medication	46 (84%)	---	---	38 (69%)	29 (52%)	---	25 (46%)	---
Adverse Event	0 (0%)	---	---	0 (0%)	0 (0%)	---	0 (0%)	---
Study 070								
Total Completed [a]	2 (4%)	---	3 (9%)	10 (20%)	12 (24%)	13 (37%)	9 (26%)	---
Total Withdrawn	48 (96%)	---	32 (91%)	40 (80%)	38 (76%)	22 (63%)	26 (74%)	---
Treatment Failure/ Rescue Medication	48 (96%)	---	31 (89%)	40 (80%)	38 (76%)	22 (63%)	26 (74%)	---
Adverse Event	0 (0%)	---	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---
							Aspirin 650 mg SD	
Study 005	(N=50)	---	---	(N=50)	---	(N=50)	(N=50)	
Total Completed[a]	3 (6%)	---	---	20 (40%)	---	22 (44%)	14 (28%)	
Total Withdrawn	47 (94%)	---	---	30 (60%)	---	28 (56%)	36 (72%)	
Lost to Follow-up	2 (4%)	---	---	---	---	1 (2%)	1 (2%)	
Treatment Failure/ Rescue Medication	45 (90%)	---	---	30 (60%)	---	27 (54%)	35 (70%)	
Adverse Event	0 (0%)	---	---	0 (0%)	---	0 (0%)	0 (0%)	

Derived from Individual Study Reports

a) Completed patient was defined as having completed evaluations through 8 hours (Study 005) or 24 hours (Studies 025, 027 and 070) without taking rescue medication.

b) One patient was discharged before the 24 hour assessment.

Table 6 presents a summary of the 422 randomized patients from the post-general and post-orthopedic surgery studies by treatment group and by completion status. The high withdrawal rates were partially related to limited length of hospital stay mandated by managed care practice.

Table 6: Reasons for Study Termination (ITT Cohort: Studies 028, and 029)

	Number of Postsurgical Patients by Treatment Group			
		Celecoxib		Darvocet-N
Study	Placebo	100 mg BID PRN	200 mg BID PRN	100 mg QID PRN
Study 028	(N=60)	(N=68)	(N=62)	(N=65)
Total Completed [a]	1 (2%)	1 (1%)	0 (0%)	1 (2%)
Total Withdrawn	59 (98%)	67 (99%)	62 (100%)	64 (98%)
Pre-Existing Violation	2 (3%)	3 (4%)	0 (0%)	0 (0%)
Protocol Noncompliance	3 (5%)	16 (24%)	10 (16%)	19 (29%)
Treatment Failure/ Rescue Medication	51 (85%)	47 (69%)	43 (69%)	44 (68%)
Adverse Event	3 (5%)	1 (1%)	9 (15%)	1 (2%)
Study 029	(N=40)	(N=45)	(N=42)	(N=40)
Total Completed [a]	1 (3%)	1 (2%)	0 (0%)	0 (0%)
Total Withdrawn	39 (98%)	44 (98%)	42 (100%)	40 (100%)
Pre-Existing Violation	2 (5%)	0 (0%)	2 (5%)	0 (0%)
Protocol Noncompliance	5 (13%)	13 (29%)	9 (21%)	13 (33%)
Treatment Failure/ Rescue Medication	27 (68%)	29 (64%)	28 (67%)	22 (55%)
Adverse Event	5 (13%)	2 (4%)	3 (7%)	5 (13%)

Derived from Individual Study Reports

a) Completed patient was defined as having completed evaluations through 5 days without taking rescue medication.

Table 7 shows a descriptive summary of the pooled Baseline demographic characteristics for all patients enrolled in the three pivotal 24-hour post-oral surgery studies (Studies 025, 027, 070).

Table 7: Pooled Baseline Demographic Characteristics for Oral Surgery Pain Patients by Treatment Group (All Randomized Patients: Studies 025, 027, and 070)

	Number of Postsurgical Patients by Treatment Group							
Baseline		Celecoxib					Naproxen Sodium	Ibuprofen
Demographic Characteristic	Placebo (N=155)	25 mg SD (N=50)	50 mg SD (N=85)	100 mg SD (N=105)	200 mg SD (N=156)	400 mg SD (N=35)	550 mg SD (N=89)	400 mg SD (N=50)
Age (years)								
Mean (Std Dev)	23.1 (4.43)	23.3 (5.72)	24.0 (5.50)	23.6 (5.61)	23.6 (5.28)	24.2 (5.97)	23.4 (5.64)	24.3 (5.48)
Range	18-43	18-46	18-45	18-50	18-47	18-41	18-52	18-50
Race/Ethnic Origin								
Asian N (%)	2 (1%)	0 (0%)	4 (5%)	3 (3%)	5 (3%)	0 (0%)	3 (3%)	2 (4%)
Black N (%)	12 (8%)	3 (6%)	9 (11%)	9 (9%)	10 (6%)	3 (9%)	4 (4%)	1 (2%)
Caucasian N (%)	95 (61%)	32 (64%)	52 (61%)	62 (59%)	93 (60%)	23 (66%)	57 (64%)	32 (64%)
Hispanic N (%)	42 (27%)	14 (28%)	20 (24%)	31 (30%)	47 (30%)	8 (23%)	25 (28%)	15 (30%)
Other N (%)	4 (3%)	1 (2%)	0 (0%)	0 (0%)	1 (<1%)	1 (3%)	0 (0%)	0 (0%)
Gender								
Male N (%)	66 (43%)	18 (36%)	32 (38%)	45 (43%)	63 (40%)	14 (40%)	38 (43%)	10 (20%)
Female N (%)	89 (57%)	32 (64%)	53 (62%)	60 (57%)	93 (60%)	21 (60%)	51 (57%)	40 (80%)

Within these studies, there were no clinically significant differences between any of the treatment groups with regard to age, race or gender with the exception of a higher proportion of females in the ibuprofen group (Study 025).

Baseline demographics for the post-general and post-orthopedic surgery studies (Studies 028, 029) are presented in Tables 8 & 9. There were no meaningful differences across treatment groups in age, race or gender.

Table 8: Baseline Demographics Characteristics for Post-Orthopedic Surgery Patients by Treatment Group (All Randomized Patients: Study 028)

Baseline Demographic Characteristic	Number of Postsurgical Patients by Treatment Group			
	Placebo (N=60)	Celecoxib 100 mg BID PRN (N=68)	Celecoxib 200 mg BID PRN (N=62)	Darvocet-N 100 mg QID PRN (N=65)
Age (years)				
Mean (Std Dev)	52.2 (16.52)	55.7 (16.35)	59.0 (16.10)	56.4 (15.73)
Range	23-87	19-82	21-86	27-84
Race/Ethnic Origin				
Asian N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black N (%)	7 (12%)	3 (4%)	1 (2%)	5 (8%)
Caucasian N (%)	51 (85%)	60 (88%)	59 (95%)	54 (83%)
Hispanic N (%)	2 (3%)	3 (4%)	2 (3%)	3 (5%)
Other N (%)	0 (0%)	2 (3%)	0 (0%)	3 (5%)
Gender				
Male N (%)	30 (50%)	37 (54%)	34 (55%)	36 (55%)
Female N (%)	30 (50%)	31 (46%)	28 (45%)	29 (45%)

Derived from Individual Study Report

Table 9: Baseline Demographics Characteristics for Post-General Surgical Patients by Treatment Group (All Randomized Patients: Study 029)

Baseline Demographic Characteristic	Number of Postsurgical Patients by Treatment Group			
	Placebo (N=40)	Celecoxib 100 mg BID PRN (N=45)	Celecoxib 200 mg BID PRN (N=42)	Darvocet-N 100 mg QID PRN (N=40)
Age (years)				
Mean (Std Dev)	44.6 (13.25)	44.4 (14.13)	48.0 (11.96)	41.5 (13.94)
Range	19-74	21-82	24-77	20-75
Race/Ethnic Origin				
Asian N (%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Black N (%)	4 (10%)	1 (2%)	3 (7%)	4 10%)
Caucasian N (%)	28 (70%)	40 (89%)	29 (69%)	30 (75%)
Hispanic N (%)	3 (8%)	4 (9%)	9 (21%)	3 (8%)
Other N (%)	5 (13%)	0 (0%)	1 (2%)	2 (5%)
Gender				
Male N (%)	4 (10%)	6 (13%)	7 (17%)	5 (13%)
Female N (%)	36 (90%)	39 (87%)	35 (83%)	35 (88%)

Derived from Individual Study Report

Methods of Data Analysis

Endpoints for Analysis of Postsurgical Studies (Single Dose Analysis)
In general, the analysis of efficacy data for each study followed the FDA's "Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models" dated January 1997. Efficacy measures for the post-oral surgery analgesia studies which were used in this ISE are:

Primary Efficacy Measures:

- Time-Specific Pain Intensity Difference (PID) (Categorical)
- Time-Specific Pain Relief (PR)
- Time-Specific Sum of PID on categorical scale and PR (PRID)
- Time to Onset of Perceptible Pain Relief
- Time to Rescue Medication

Secondary Efficacy Measures:

- Time-Specific Pain Intensity Difference (VAS)
- Summed Pain Intensity Difference, (SPID), for the sum of the PID scores through the first 3, 6, 8, 10 and 12 hours, respectively
- Total Pain Relief (TOTPAR) for the sum of the PR scores through the first 3, 6, 8, 10 and 12 hours, respectively
- Summed PRID scores (SPRID) for the sum of the PRID scores through the first 3, 6, 8, 10 and 12 hours, respectively
- Time to First Experienced 50% Pain Relief;
- Proportion of patients who experienced 50% pain relief;
- Proportion of patients who experienced 100% pain relief defined as complete pain relief (PR=4) and pain intensity (categorical) rating of none (PI=0).

Additional secondary efficacy variables were collected in the individual studies. These variables include maximum pain intensity (categorical scale), maximum pain relief, and APS pain measure (for Study 028) and Patients Global Evaluation (for Studies 005 and 028). These variables were analyzed in the individual study reports.

Patient Population Analyzed - Postsurgical Studies
Analyses in this ISE were based on the ITT Cohort. The ITT Cohort was defined as all randomized patients who took the dose of study drug with the following exceptions: patients who required rescue medication prior to the one-hour assessment were excluded from the efficacy analysis. In addition, if two consecutive scheduled pain assessments in the first two hours were missed, and therefore obtained by interpolation from the same two observed data points for any patient, that patient was excluded from the analyses.

Timepoints Analyzed

Patient's pain was assessed at Baseline and at 0.25, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours postdose (the exception was Study 005 which only went through 8 hours postdose). Time-specific pain measurements were analyzed at all these timepoints.

Missing Values

For each individual study, the results reported in the clinical reports were analyzed using both the LOCF (last observation carried forward) and BOCF (baseline observation carried forward) approaches for imputing pain intensity and pain relief data after the patient took rescue medication.

Presentation of Data

Several tables employ the "ABC" method of designating statistical significance. The following example will serve to demonstrate the interpretation of this method.

If:

Treatment 1	A
Treatment 2	AB
Treatment 3	BC
Treatment 4	C

One would conclude that treatment 1 is significantly different from treatments 3 and 4 but not treatment 2, and that treatments 2 and 3 are not significantly different from each other, but 2 is significantly different from 4.

Comparison of Celecoxib to Placebo in Postsurgical Studies

Pain Intensity Difference and Pain Relief (PRID); Pain Relief (PR) and Pain Intensity Difference (PID, Categorical)

Mean Pain Intensity Difference and Pain Relief (PRID) Scores were calculated as the sum of the Pain Relief (PR) Score and Pain Intensity Difference (PID) Score. The best possible score was 7 (complete pain relief [PR=4] and change from severe pain at Baseline to no pain [PID=3]. The worst possible score was -1 (no pain relief [PR=0] and change from moderate pain at Baseline to severe pain [PID=-1]).

Mean Pain Relief (PR) scores were reported on a scale of 0 to 4 with 0 indicating no pain relief and 4 indicating complete pain relief.

Mean PID (Categorical) Scores were calculated by subtracting the pain intensity at a specific assessment time from the Baseline pain intensity. Scores could range from -1 (worst possible score) to 3 (best possible score).

Text Tables 83-87 present the mean PRID scores (BOCF method of imputation) for Studies 025, 027, 070, and 028. The mean PR and PID scores (BOCF), are present in the individual study reports.

In the double-blind post-oral surgery studies, celecoxib at doses 200 mg SD (Studies 025, 027 and 070), and 400 mg SD (Study 070) showed statistically significantly greater improvement compared to placebo beginning by 1.0 hour postdose and continuing through 8.0 hours postdose for the PRID (tables 83-85). In Studies 025 and 027 differences from placebo were seen by 0.75 hours postdose. Celecoxib at a dose of 100 mg SD (Studies 027 and 070), showed similar results except in Study 027 where the 100 mg dose separated statistically from placebo only up to 7 hours postdose. Analogous results were observed for the PID and PR for all three doses. Celecoxib in doses of 25 mg and 50 mg was subtherapeutic.

Ibuprofen 400 mg and naproxen sodium 550 mg validated the dental pain studies by showing statistically significant superiority over placebo in all pain measurements beginning at 0.75 hour postdose and continuing through 9 hours (8 hours in PR scores) for the ibuprofen and 24 hours for the naproxen sodium. Also, these active controls showed consistent, statistically significant superiority in all pain measurements over celecoxib. This significantly better efficacy began at 0.75 hour postdose (0.5 hour for naproxen in study # 027) and continued through 3 to 4 hours for all of the proposed therapeutic doses of celecoxib.

The post-orthopedic surgery study (Study 028) failed to detect statistically significant treatment differences between celecoxib and placebo (tables 86-87). In this study for single dose responses based on the BOCF analyses, celecoxib at doses of 100 mg SD and 200 mg SD was associated with numerically greater mean PRID (Text Table 86), PR and PID scores compared with placebo from 1.5-8 hours postdose, however, these differences were not statistically significant.

For the multiple dose analysis, again, efficacy scores with celecoxib 100 mg BID PRN or 200 mg BID PRN were numerically but not statistically significant superior to placebo, beginning at about 1 hour and continuing through the entire 24 hour postdose period. Using the BOCF method of imputation, celecoxib 200 mg BID PRN was significantly different from placebo at only a few and inconsistent timepoints for all of the measures of efficacy.

Darvocet-N which was used as an active control in this study did not separate from placebo as well suggesting that this pain model may not be appropriate for the tested medications and requires the highest degree of analgesia (i.e., opiates).

Table 83: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 025

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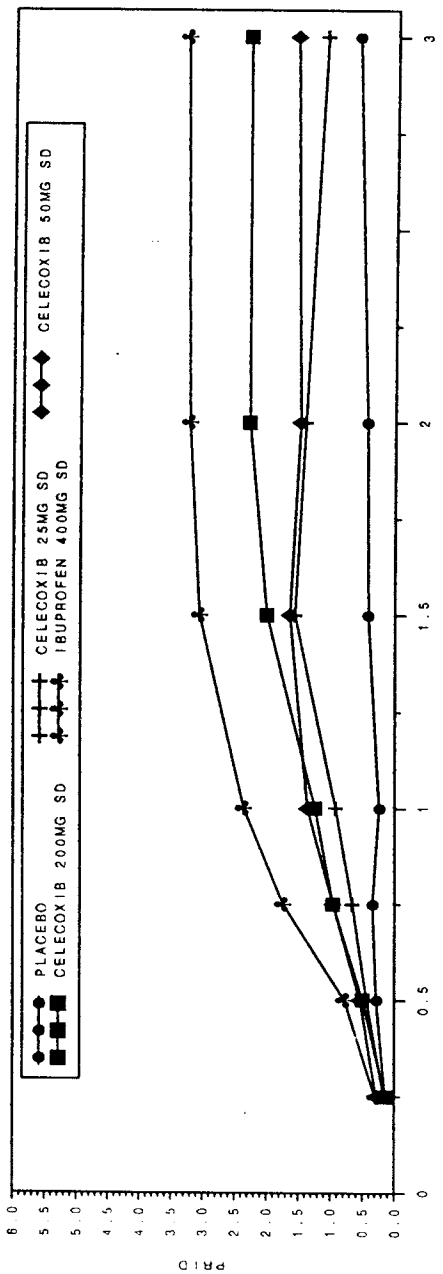
CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 83
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED)
MEANS, (STANDARD DEVIATIONS). SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - STUDY 025)

MEAN PRID SCORES OVER TIME



TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
IBUPROFEN 400MG SD	0.30 (0.84) 50(e) A(e)	0.78 (1.04) 50 A	1.74 (1.59) 50 A	2.36 (1.84) 50 A	3.06 (2.13) 44 A	3.22 (2.22) 40 A	3.28 (2.50) 35 A
CELECOXIB 200MG SD	0.14 (0.70) 50 A	0.50 (1.13) 50 A	0.96 (1.54) 50 B	1.24 (1.67) 50 B	2.00 (2.16) 40 B	2.28 (2.38) 28 B	2.30 (2.47) 27 B
CELECOXIB 50MG SD	0.28 (0.67) 50 A	0.54 (0.95) 50 A	0.96 (1.59) 50 B	1.38 (1.94) 50 B	1.64 (1.84) 38 B	1.48 (2.03) 26 C	1.56 (2.17) 21 BC
CELECOXIB 25MG SD	0.16 (0.98) 50 A	0.44 (1.11) 50 A	0.66 (1.38) 50 BC	0.92 (1.55) 50 B	1.56 (1.86) 32 B	1.40 (1.82) 22 C	1.10 (1.76) 18 CD
PLACEBO	0.14 (0.67) 50 A	0.28 (1.08) 50 A	0.34 (1.15) 50 C	0.24 (1.19) 50 C	0.42 (1.07) 24 C	0.44 (1.25) 12 D	0.60 (1.54) 8 D
TREATMENT P-VALUE (b)	0.669	0.151	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
TRT-BASELINE P-VALUE (c)	0.250	0.580	0.918	0.723	0.603	0.432	0.779
GENDER P-VALUE (d)	0.440	0.164	0.006	0.012	0.029	0.284	0.235
RMS ERROR (b)	0.774	1.052	1.440	1.624	1.853	1.985	2.126

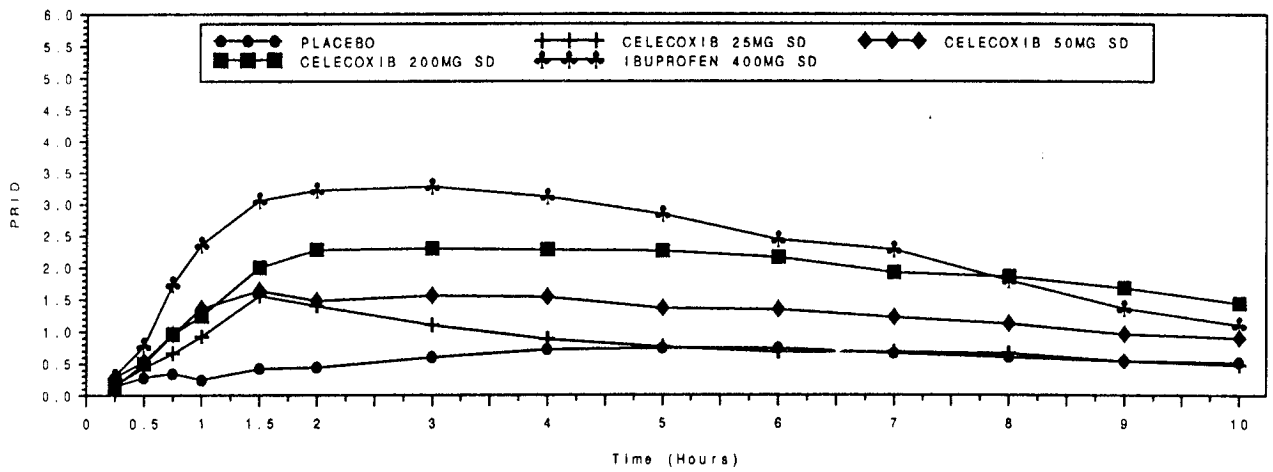
(a) Sample size is not extrapolated.
(b) Model: PRID = mu + Ti + Pi(0)j + error.
(c) Model: PRID = mu + Ti + Pi(0)j + Gi + error.
(d) Based on model (b). LSmeans with the same letter are not significantly different from each other.

DRAFT

CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 83
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - STUDY 025)

MEAN PRID SCORES OVER TIME



ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00	9.00	10.00
IBUPROFEN 400MG SD	3.12 (2.54) 34(a) A(e)	2.84 (2.68) 33 A	2.44 (2.58) 28 A	2.28 (2.63) 26 A	1.80 (2.39) 23 A	1.36 (2.16) 18 A	1.10 (2.08) 14 A
CELECOXIB 200MG SD	2.28 (2.62) 24 AB	2.26 (2.57) 24 A	2.16 (2.60) 24 AB	1.92 (2.50) 23 AB	1.86 (2.58) 20 A	1.68 (2.48) 19 A	1.44 (2.32) 18 A
CELECOXIB 50MG SD	1.54 (2.17) 20 BC	1.36 (2.08) 19 B	1.34 (2.12) 17 BC	1.22 (2.11) 16 BC	1.12 (2.13) 13 AB	0.96 (1.85) 12 AB	0.90 (1.94) 11 A
CELECOXIB 25MG SD	0.88 (1.75) 13 C	0.76 (1.70) 10 B	0.68 (1.66) 8 C	0.68 (1.73) 7 C	0.66 (1.69) 7 B	0.54 (1.53) 6 B	0.48 (1.36) 6 A
PLACEBO	0.72 (1.75) 8 C	0.74 (1.80) 8 B	0.74 (1.80) 8 C	0.66 (1.70) 8 C	0.60 (1.69) 6 B	0.54 (1.62) 6 B	0.52 (1.62) 5 A
TREATMENT p-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	0.004	0.015	0.075
TRT*BASELINE p-VALUE (c)	0.702	0.578	0.631	0.493	0.556	0.326	0.435
GENDER p-VALUE (d)	0.395	0.257	0.262	0.202	0.280	0.418	0.414
RMS ERROR (b)	2.200	2.207	2.190	2.171	2.131	1.962	1.898

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + TI + PI(0)j + error.
(c) Model: PRID = mu + TI + PI(0)j + TI*PI(0)j + error.
(d) Model: PRID = mu + TI + PI(0)j + GI + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

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CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 83

PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID) CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - STUDY 025)

MEAN PRID SCORES OVER TIME

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	24.00
IBUPROFEN 400MG SD	0.90 (1.95) 10 A(e)	0.78 (1.69) 10 A	0.76 (1.79) 7 AB
CELECOXIB 200MG SD	1.38 (2.37) 15 A	1.44 (2.43) 14 A	1.48 (2.57) 13 A
CELECOXIB 50MG SD	0.82 (1.89) 9 A	0.82 (1.89) 9 A	0.70 (1.84) 7 B
CELECOXIB 25MG SD	0.54 (1.53) 6 A	0.48 (1.48) 6 A	0.40 (1.40) 4 B
PLACEBO	0.48 (1.66) 4 A	0.48 (1.66) 4 A	0.48 (1.66) 4 B

TREATMENT P-VALUE (b)	0.157	0.083	0.048
TRT*BASELINE P-VALUE (c)	0.466	0.314	0.283
GENDER P-VALUE (d)	0.521	0.439	0.740
RMS ERROR (e)	1.904	1.860	1.896

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + Ti + Pi(0)j + error. (b) Model: PRID = mu + Ti + Pi(0)j + Gi + error.
(c) Based on model (b) LSmeans treatments with the same
letter are not significantly different from each other.

Table 84: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 027

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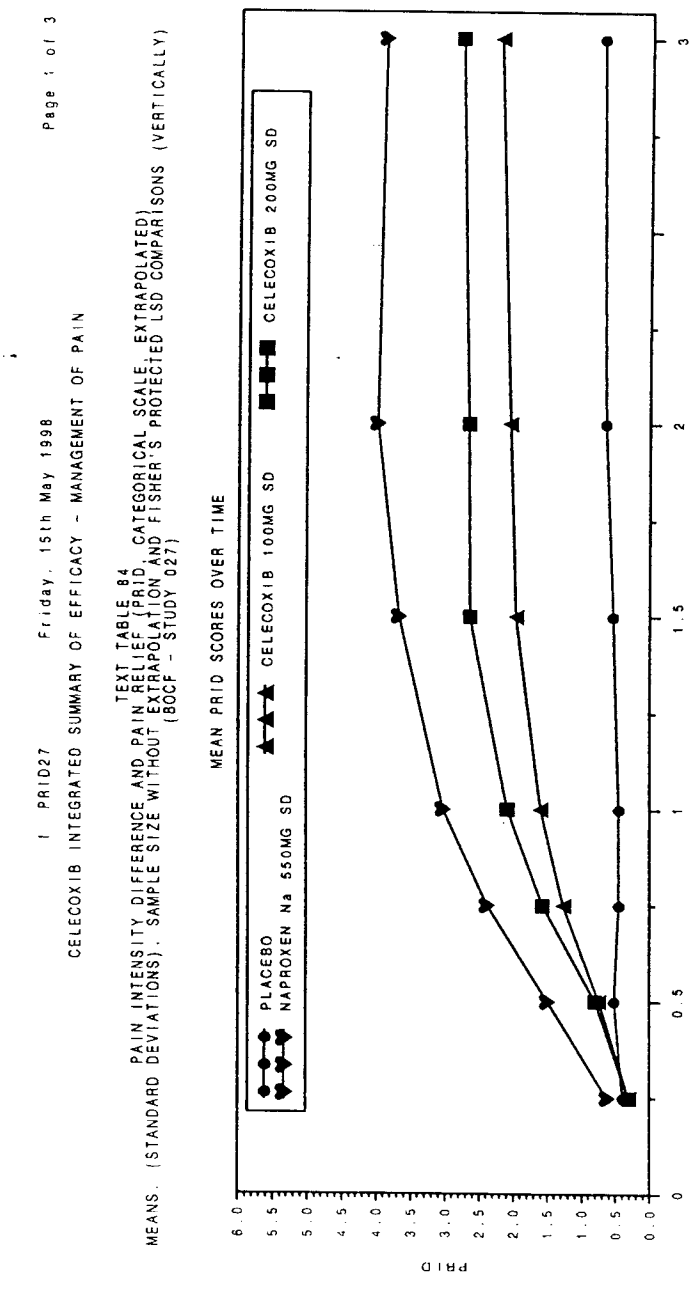
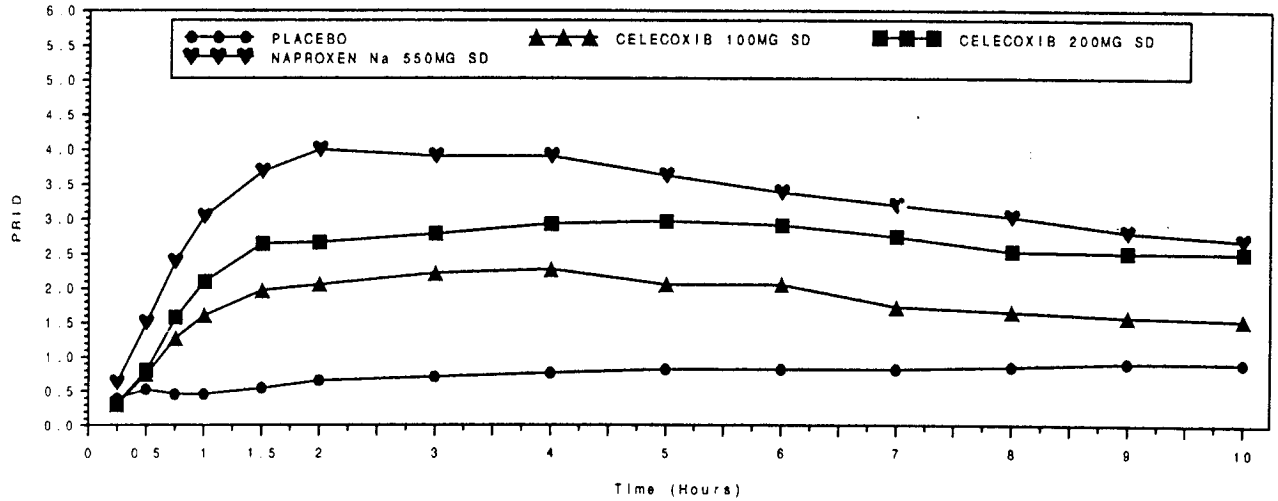


DRAFT

CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 84
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - STUDY 027)

MEAN PRID SCORES OVER TIME



ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00	9.00	10.00
NAPROXEN Na 550MG SD	3.91 (2.09) 45(a) A(e)	3.63 (2.23) 42 A	3.39 (2.37) 40 A	3.20 (2.41) 38 A	3.04 (2.45) 37 A	2.81 (2.40) 35 A	2.70 (2.39) 34 A
CELECOXIB 200MG SD	2.93 (2.56) 37 B	2.96 (2.62) 36 A	2.91 (2.65) 35 AB	2.75 (2.62) 33 A	2.54 (2.62) 33 A	2.52 (2.64) 31 A	2.52 (2.72) 28 A
CELECOXIB 100MG SD	2.27 (2.51) 30 B	2.05 (2.40) 27 B	2.05 (2.50) 25 B	1.73 (2.34) 23 B	1.65 (2.38) 21 B	1.58 (2.39) 18 B	1.55 (2.36) 19 B
PLACEBO	0.76 (1.76) 10 C	0.82 (1.93) 9 C	0.82 (1.93) 9 C	0.82 (1.93) 9 C	0.85 (2.01) 9 B	0.91 (2.11) 9 B	0.91 (2.11) 9 B
TREATMENT p-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
TRT*BASELINE p-VALUE (c)	0.403	0.457	0.437	0.624	0.571	0.650	0.555
GENDER p-VALUE (d)	0.517	0.740	0.499	0.775	0.662	0.533	0.546
RMS ERROR (b)	2.259	2.317	2.383	2.349	2.382	2.398	2.407

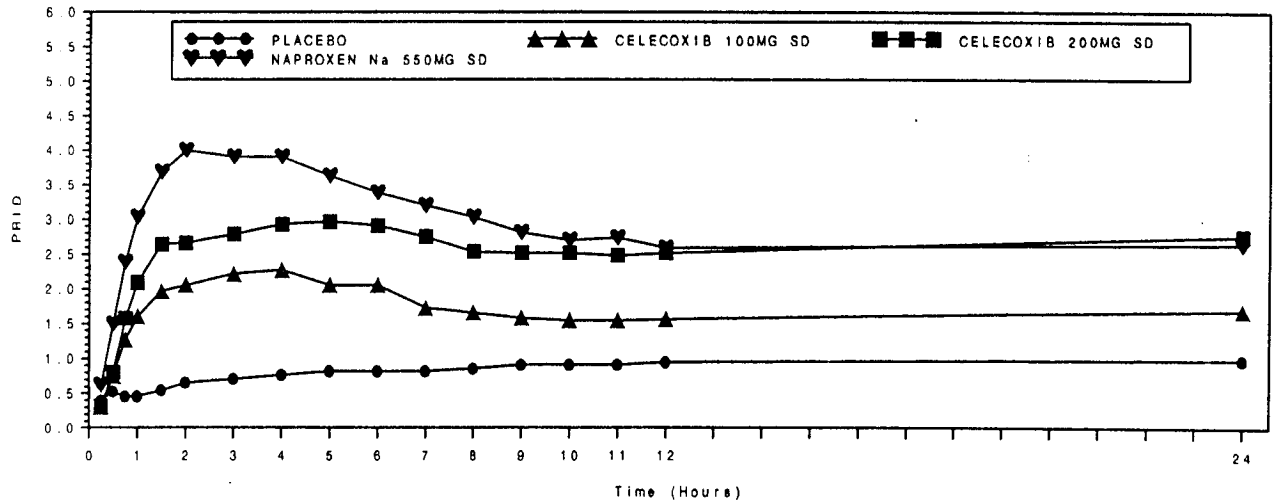
(a) Sample size is not extrapolated.
(b) Model: PRID = mu + TI + PI(0)j + error.
(c) Model: PRID = mu + TI + PI(0)j + TI*PI(0)j + error.
(d) Model: PRID = mu + TI + PI(0)j + GI + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

DRAFT

CELECOXIB INTEGRATED SUMMARY OF EFFICACY – MANAGEMENT OF PAIN

TEXT TABLE 84
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF – STUDY 027)

MEAN PRID SCORES OVER TIME



TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	24.00
NAPROXEN Na 550MG SD	2.74 (2.40) 33(a) A(e)	2.59 (2.43) 31 A	2.85 (2.73) 28 AB
CELECOXIB 200MG SD	2.48 (2.78) 29 A	2.52 (2.82) 27 A	2.77 (2.99) 27 A
CELECOXIB 100MG SD	1.55 (2.48) 16 B	1.56 (2.49) 17 B	1.69 (2.64) 17 BC
PLACEBO	0.91 (2.11) 9 B	0.95 (2.20) 9 B	0.98 (2.26) 9 C
TREATMENT p-VALUE (b)	< 0.001	0.001	0.001
TRT*BASELINE p-VALUE (c)	0.405	0.445	0.284
GENDER p-VALUE (d)	0.445	0.389	0.241
RMS ERROR (b)	2.456	2.499	2.672

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + Ti + PI(0)j + error.
(c) Model: PRID = mu + Ti + PI(0)j + Ti*PI(0)j + error.
(d) Model: PRID = mu + Ti + PI(0)j + Gi + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Table 85: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 070

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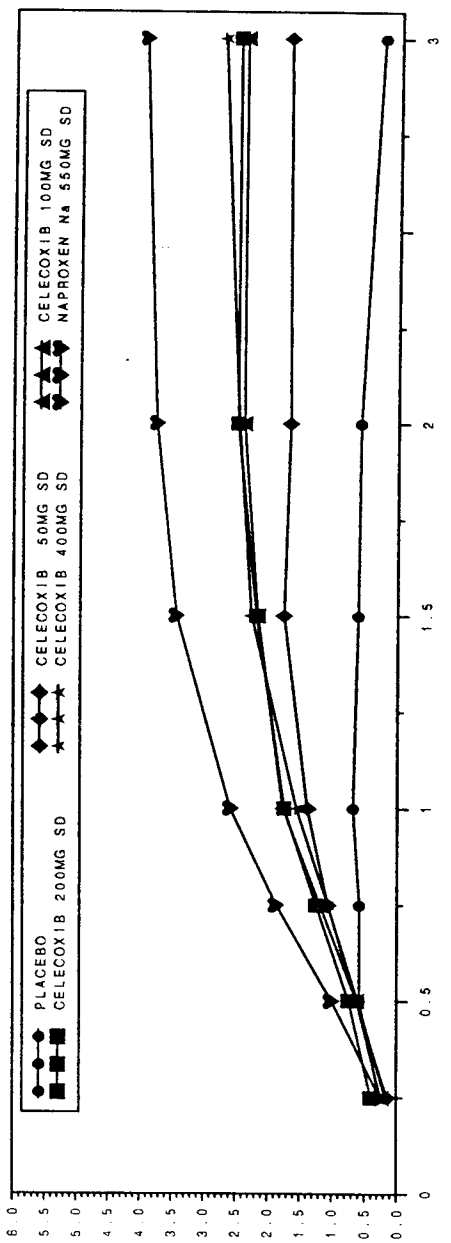
CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 85
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - STUDY 070)

MEAN PRID SCORES OVER TIME



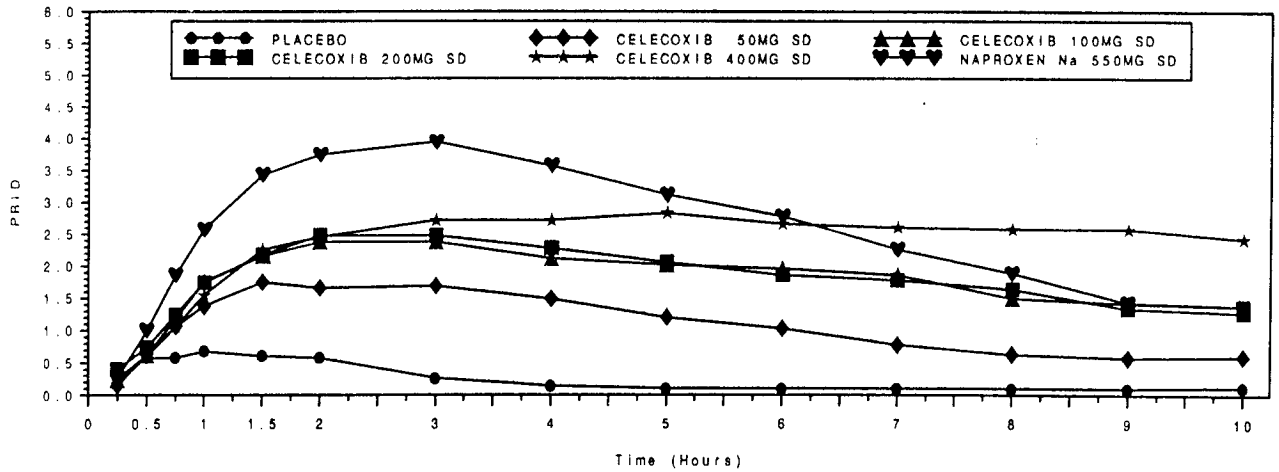
TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
NAPROXEN Na 550MG SD	0.26 (0.82) 35(a) A(e)	1.00 (1.21) 35 A	1.86 (1.56) 35 A	2.57 (2.00) 35 A	3.43 (2.21) 31 A	3.74 (2.36) 30 A	3.94 (2.46) 28 A
CELECOXIB 400MG SD	0.17 (0.71) 35 A	0.60 (1.06) 35 A	1.08 (1.63) 35 B	1.54 (1.80) 35 B	2.26 (2.17) 25 B	2.46 (2.21) 24 B	2.71 (2.62) 21 B
CELECOXIB 200MG SD	0.40 (0.73) 50 A	0.74 (1.19) 50 A	1.24 (1.65) 50 B	1.74 (1.94) 50 B	2.18 (2.10) 35 B	2.48 (2.40) 30 B	2.48 (2.38) 30 B
CELECOXIB 100MG SD	0.24 (0.72) 50 A	0.62 (1.12) 50 A	1.18 (1.79) 50 B	1.76 (2.11) 50 B	2.16 (2.35) 34 B	2.38 (2.55) 28 B	2.38 (2.68) 25 B
CELECOXIB 50MG SD	0.14 (0.65) 35 A	0.63 (1.33) 35 A	1.06 (1.49) 35 B	1.37 (1.83) 35 BC	1.74 (2.06) 25 B	1.66 (2.21) 16 B	1.69 (2.31) 14 B
PLACEBO	0.26 (0.63) 50 A	0.58 (1.11) 50 A	0.58 (1.33) 50 B	0.68 (1.50) 50 C	0.61 (1.43) 19 C	0.58 (1.43) 13 C	0.26 (0.94) 5 C
TREATMENT p-VALUE (b)	0.817	0.386	0.009	< 0.001	< 0.001	< 0.001	< 0.001
TRT*BASELINE p-VALUE (c)	0.848	0.298	0.244	0.130	0.658	0.299	0.905
GENDER p-VALUE (d)	0.276	0.404	0.310	0.229	0.362	0.387	0.476
RMS ERROR (b)	0.692	1.150	1.568	1.857	2.040	2.205	2.272

(a) Sample size is not extrapolated
(c) Model: PRID = mu + Ti + Pi(0)j + error.
(e) Based on model: LSmeans of treatments with the same letter are not significantly different from each other.
(b) Model: PRID = mu + Ti + Pi(0)j + Gl + error.
(d) Model: PRID = mu + Ti + Pi(0)j + Gl + error.

CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 85
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - STUDY 070)

MEAN PRID SCORES OVER TIME



ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00	9.00	10.00
NAPROXEN Na 550MG SD	3.57 (2.50) 28(a) A(e)	3.11 (2.56) 25 A	2.77 (2.64) 21 A	2.26 (2.47) 20 A	1.89 (2.51) 16 AB	1.43 (2.24) 13 BC	1.37 (2.26) 10 B
CELECOXIB 400MG SD	2.71 (2.75) 20 AB	2.83 (2.79) 19 AB	2.88 (2.89) 19 A	2.60 (2.72) 18 A	2.57 (2.66) 18 A	2.57 (2.70) 18 A	2.43 (2.62) 18 A
CELECOXIB 200MG SD	2.28 (2.46) 27 BC	2.06 (2.54) 24 BC	1.86 (2.43) 21 AB	1.78 (2.41) 20 A	1.64 (2.35) 18 AB	1.34 (2.21) 16 BC	1.28 (2.24) 14 B
CELECOXIB 100MG SD	2.12 (2.68) 23 BC	2.02 (2.61) 21 BC	1.96 (2.60) 21 AB	1.86 (2.64) 19 A	1.50 (2.39) 16 BC	1.42 (2.34) 15 B	1.38 (2.26) 15 B
CELECOXIB 50MG SD	1.49 (2.19) 13 C	1.20 (2.01) 11 C	1.03 (1.92) 10 BC	0.77 (1.72) 8 B	0.63 (1.54) 6 CD	0.57 (1.52) 5 CD	0.60 (1.67) 5 BC
PLACEBO	0.14 (0.64) 3 D	0.10 (0.58) 2 D	0.10 (0.58) 2 C	0.10 (0.58) 2 B	0.10 (0.58) 2 D	0.10 (0.58) 2 D	0.12 (0.63) 2 C
TREATMENT p-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
TRT*BASELINE p-VALUE (c)	0.773	0.496	0.542	0.184	0.255	0.107	0.147
GENDER p-VALUE (d)	0.998	0.703	0.610	0.532	0.164	0.111	0.076
RMS ERROR (b)	2.284	2.283	2.240	2.202	2.106	2.027	2.021

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + Ti + PI(0)j + error.
(c) Model: PRID = mu + Ti + PI(0)j + Ti*PI(0)j + error
(d) Model: PRID = mu + Ti + PI(0)j + GI + error
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other

CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 85
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID) CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(80CF - STUDY 070)

MEAN PRID SCORES OVER TIME

ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	11.00	12.00	24.00
NAPROXEN Na 550MG SD	1.23 (2.12) 10(a) B(e)	1.26 (2.23) 9 B	1.46 (2.54) 9 AB
CELECOXIB 400MG SD	2.43 (2.70) 17 A	2.37 (2.89) 17 A	2.06 (2.79) 13 A
CELECOXIB 200MG SD	1.16 (2.08) 14 B	1.14 (2.13) 12 B	1.26 (2.32) 12 A
CELECOXIB 100MG SD	1.32 (2.20) 15 B	1.24 (2.16) 14 B	1.08 (2.24) 10 AB
CELECOXIB 50MG SD	0.54 (1.62) 5 BC	0.49 (1.54) 4 BC	0.49 (1.62) 3 BC
PLACEBO	0.12 (0.63) 2 C	0.12 (0.63) 2 C	0.20 (1.01) 2 C
TREATMENT P-VALUE (b)	< 0.001	< 0.001	0.001
TRTBASELINE P-VALUE (c)	0.168	0.219	0.053
GENDER P-VALUE (d)	0.067	0.041	0.028
RMS ERROR (b)	1.960	1.967	2.110

(a) Sample size is not extrapolated.
(b) Model: PRID = mu + Ti + Pi(0)j + error.
(c) Model: PRID = mu + Ti + Pi(0)j + Ti*Pi(0)j + error
(d) Model: PRID = mu + Ti + Pi(0)j + Gi + error.
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

Table 86: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated) - BOCF - Study 028 - Single Dose

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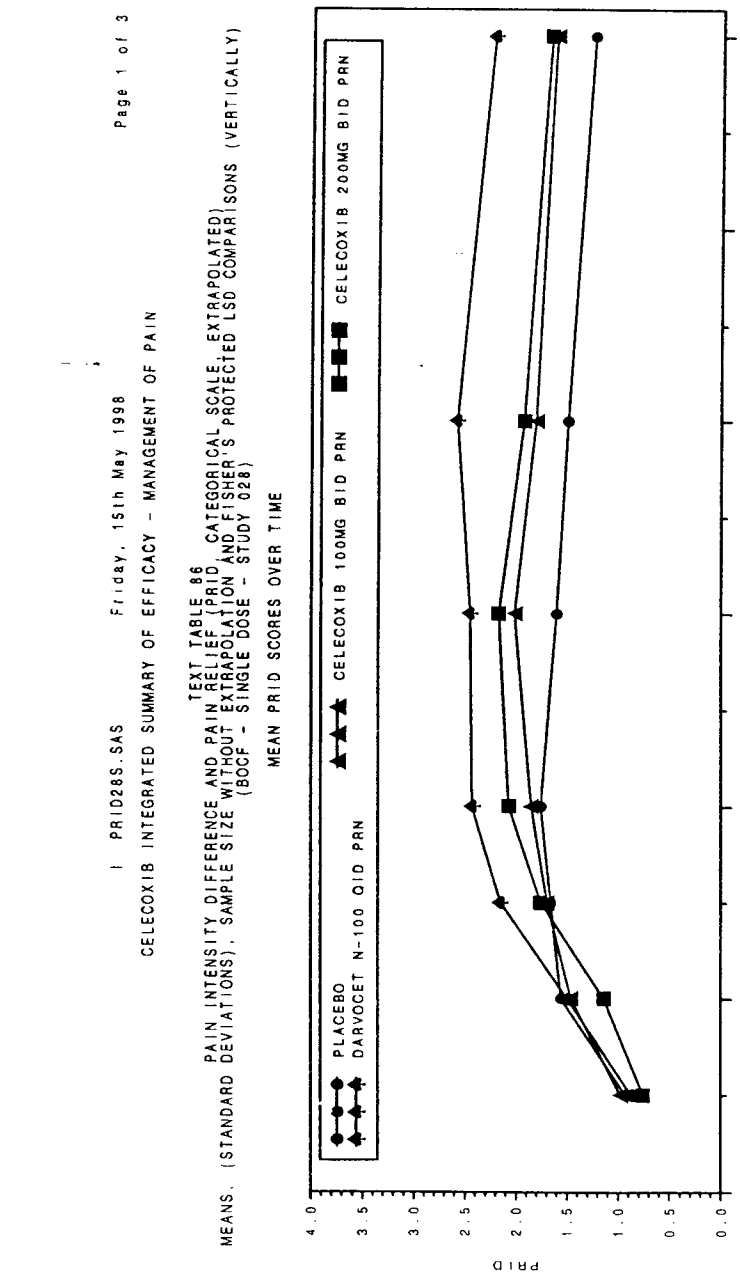
CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 86
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - SINGLE DOSE - STUDY 028)

MEAN PRID SCORES OVER TIME



TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.87 (1.29) 61 A(a)	1.50 (1.63) 61 A	2.15 (1.96) 60 A	2.43 (2.06) 61 A	2.45 (2.17) 53 A	2.58 (2.21) 47 A	2.23 (2.21) 43 A
CELECOXIB 200MG BID PRN	0.76 (1.08) 58 A	1.14 (1.50) 57 A	1.76 (1.81) 57 A	2.07 (2.07) 58 A	2.17 (2.08) 46 A	1.92 (1.95) 38 B	1.87 (2.04) 33 AB
CELECOXIB 100MG BID PRN	0.98 (1.30) 66 A	1.46 (1.61) 67 A	1.70 (1.72) 64 A	1.85 (1.82) 67 A	2.01 (1.88) 56 A	1.81 (1.98) 46 B	1.62 (1.90) 38 B
PLACEBO	0.93 (1.27) 59 A	1.56 (1.67) 59 A	1.66 (1.65) 58 A	1.75 (1.77) 58 A	1.60 (1.77) 51 A	1.49 (1.84) 48 B	1.25 (1.86) 34 B
TREATMENT P-VALUE (b)	0.814	0.417	0.254	0.149	0.071	0.012	0.037
TRT*BASELINE P-VALUE (c)	0.081	0.265	0.270	0.256	0.468	0.856	0.341
TRT*CENTER P-VALUE (c)	0.681	0.861	0.500	0.625	0.073	0.299	0.265
GENDER P-VALUE (d)	0.901	0.903	0.713	0.312	0.455	0.320	0.687
BASELINE P-VALUE (b)	0.536	0.414	0.862	0.684	0.314	0.345	0.680
CENTER P-VALUE (b)	0.094	0.332	0.056	0.084	< 0.001	0.006	0.010
SURGERY TYPE P-VALUE (d)	0.149	0.594	0.586	0.893	0.690	0.914	0.935
RMS ERROR (b)	1.226	1.601	1.763	1.909	1.891	1.941	1.955

(a) Sample size is not extrapolated
(b) Model: PRID = mu + Ti + P(i(j)) + center + error
(c) Model: PRID = mu + Ti + P(i(j)) + effect term + center + error
(d) Based on model (b), LSmeans (0) treatments with the same letter are not significantly different from each other

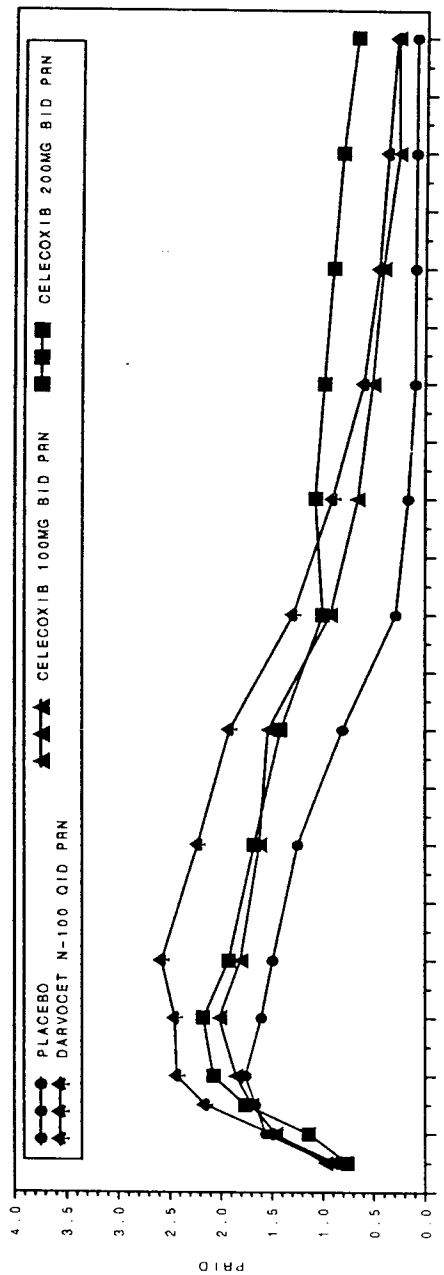
1 PRID28S.SAS Friday, 15th May 1998 Page 2 of 3

CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 86

PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - SINGLE DOSE - STUDY 028)

MEAN PRID SCORES OVER TIME



ASSESSMENT TIME POINTS (IN HOURS)

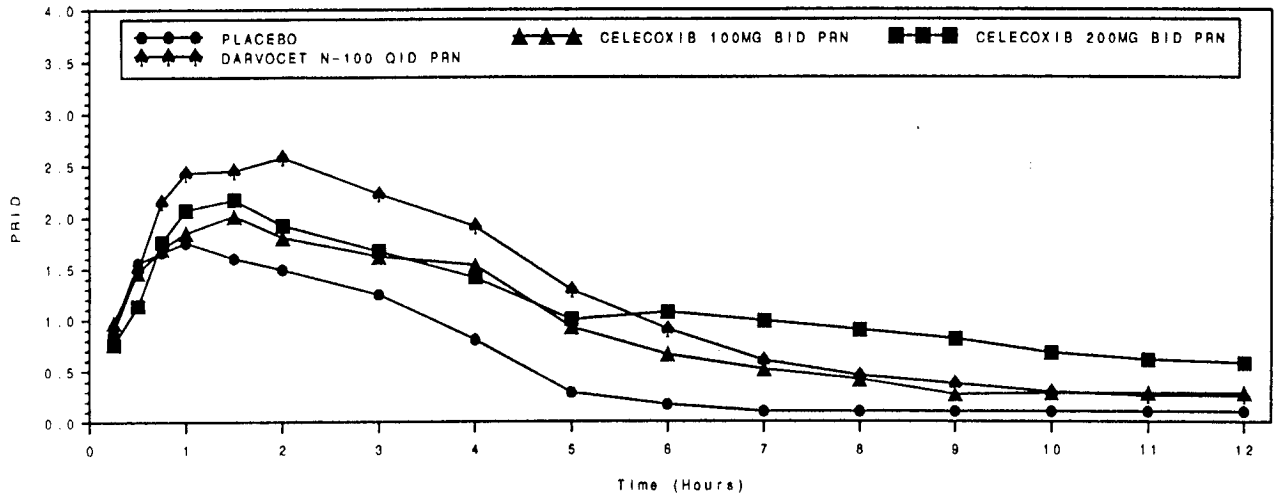
TREATMENT	4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCET N-100 QID PRN	1.91 (2.18) 39(a) A(e)	1.29 (2.11) 20 A	0.90 (1.92) 13 A	0.60 (1.62) 9 AB	0.45 (1.53) 8 A	0.37 (1.35) 5 AB	0.29 (1.23) 4 A
CELECOXIB 200MG BID PRN	1.41 (2.08) 27 AB	1.00 (2.01) 14 AB	1.07 (2.13) 12 A	0.98 (2.04) 10 A	0.90 (1.99) 9 A	0.81 (1.88) 9 A	0.67 (1.65) 7 A
CELECOXIB 100MG BID PRN	1.53 (1.95) 36 AB	0.93 (1.77) 18 B	0.86 (1.68) 12 AB	0.51 (1.40) 9 AB	0.41 (1.41) 6 A	0.27 (1.19) 4 B	0.28 (1.18) 2 A
PLACEBO	0.81 (1.53) 24 B	0.29 (1.05) 5 B	0.17 (0.87) 3 B	0.10 (0.78) 1 B	0.10 (0.78) 1 A	0.10 (0.78) 1 B	0.10 (0.78) 1 A
TREATMENT p-VALUE (b)	0.013	0.007	0.029	0.037	0.072	0.049	0.156
TRT*BASELINE p-VALUE (c)	0.139	0.349	0.410	0.199	0.154	0.261	0.581
TRT*CENTER p-VALUE (c)	0.049	0.062	0.012	0.002	0.001	0.039	0.318
GENDER p-VALUE (d)	0.374	0.743	0.973	0.838	0.983	0.466	0.270
BASELINE p-VALUE (b)	0.662	0.239	0.201	0.224	0.266	0.342	0.380
CENTER p-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001	0.002	0.005	0.044
SURGERY TYPE p-VALUE (d)	0.705	0.252	0.632	0.599	0.545	0.391	0.390
RMS ERROR (b)	1.857	1.607	1.565	1.417	1.434	1.308	1.224

(a) Sample size is not extrapolated
(c) Model: PRID = mu + Ti + Pj(0)j + interaction term + center + error (b) Model: PRID = mu + Ti + Pj(0)j + center + error
(e) Based on model (b) LSmeans (d) Model: PRID = mu + Ti + Pj(0)j + center + error + effect(term +
Treatments with the same letter are not significantly different from each other.

CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 86
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - SINGLE DOSE - STUDY 028)

MEAN PRID SCORES OVER TIME



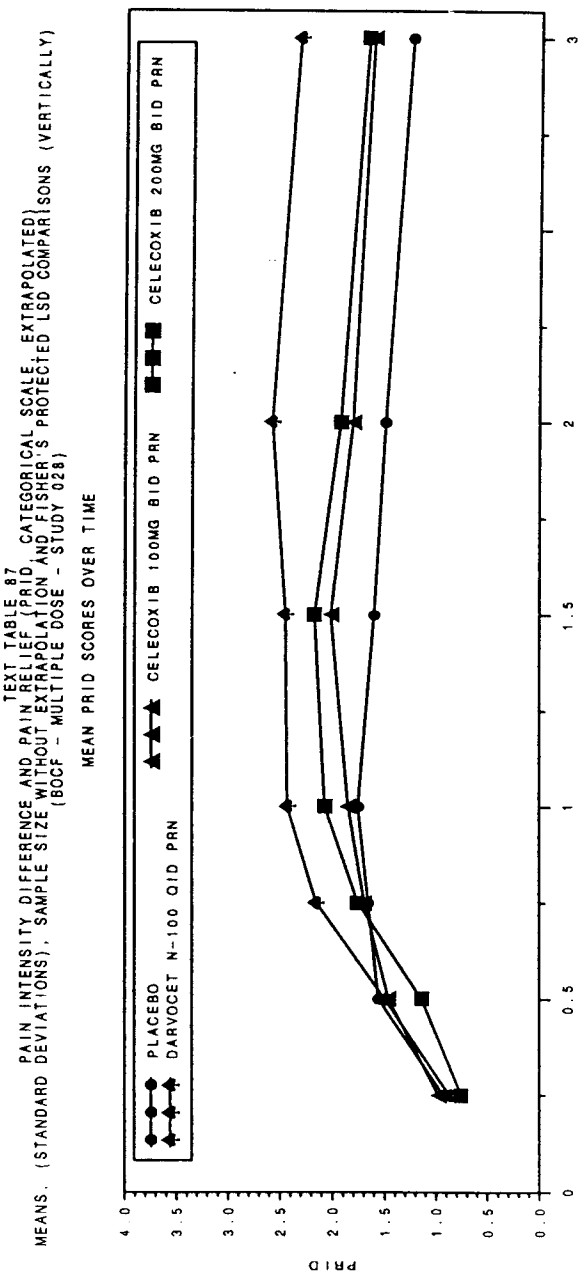
ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	11.00	12.00
DARVOCET N-100 QID PRN	0.26 (1.21) 3(a) A(e)	0.26 (1.21) 3 A
CELECOXIB 200MG BID PRN	0.61 (1.60) 6 A	0.57 (1.53) 6 A
CELECOXIB 100MG BID PRN	0.28 (1.18) 2 A	0.28 (1.18) 2 A
PLACEBO	0.10 (0.78) 1 A	0.10 (0.78) 1 A

TREATMENT p-VALUE (b)	0.272	0.318
TRT*BASELINE p-VALUE (c)	0.602	0.525
TRT*CENTER p-VALUE (c)	0.593	0.743
GENDER p-VALUE (d)	0.207	0.240
BASELINE p-VALUE (b)	0.480	0.376
CENTER p-VALUE (b)	0.066	0.126
SURGERY TYPE p-VALUE (d)	0.348	0.243
RMS ERROR (b)	1.207	1.190

(a) Sample size is not extrapolated
(b) Model: PRID = mu + Ti + PI(0)j + center + error
(c) Model: PRID = mu + Ti + PI(0)j + interaction term + center + error
(d) Model: PRID = mu + Ti + PI(0)j + effect term + center + error
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other

Table 87: Pain Intensity Difference and Pain Relief (PRID, Categorical Scale, Extrapolated)-BOCF-Study 028, Multiple Dose



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CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 87
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - MULTIPLE DOSE - STUDY 028)

MEAN PRID SCORES OVER TIME

TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 0.25	0.50	0.75	1.00	1.50	2.00	3.00
DARVOCET N-100 QID PRN	0.87 (1.29) 81 (a) A(e)	1.50 (1.63) 81 A	2.15 (1.96) 80 A	2.43 (2.06) 81 A	2.45 (2.17) 53 A	2.58 (2.21) 47 A	2.32 (2.24) 44 A
CELECOXIB 200MG BID PRN	0.76 (1.08) 58 A	1.14 (1.50) 57 A	1.78 (1.81) 57 A	2.07 (2.07) 58 A	2.17 (2.08) 48 A	1.92 (1.95) 39 B	1.87 (2.04) 33 B
CELECOXIB 100MG BID PRN	0.98 (1.30) 66 A	1.46 (1.61) 67 A	1.70 (1.72) 64 A	1.85 (1.82) 67 A	2.01 (1.88) 56 A	1.81 (1.88) 46 B	1.62 (1.90) 38 B
PLACEBO	0.93 (1.27) 59 A	1.56 (1.67) 59 A	1.66 (1.65) 58 A	1.75 (1.77) 58 A	1.60 (1.77) 51 A	1.49 (1.84) 48 B	1.25 (1.86) 34 B
TREATMENT p-VALUE (b)	0.814	0.417	0.254	0.149	0.071	0.012	0.016
TRT*BASELINE p-VALUE (c)	0.081	0.265	0.270	0.256	0.468	0.850	0.372
TRT*CENTER p-VALUE (c)	0.681	0.851	0.500	0.625	0.079	0.299	0.159
GENDER p-VALUE (d)	0.901	0.903	0.713	0.312	0.465	0.320	0.851
BASELINE p-VALUE (b)	0.536	0.414	0.862	0.684	0.314	0.345	0.512
CENTER p-VALUE (b)	0.094	0.332	0.056	0.084	< 0.001	0.006	0.009
SURGERY TYPE p-VALUE (d)	0.149	0.594	0.586	0.893	0.690	0.914	0.823
RMS ERROR (b)	1.226	1.601	1.763	1.909	1.891	1.941	1.961

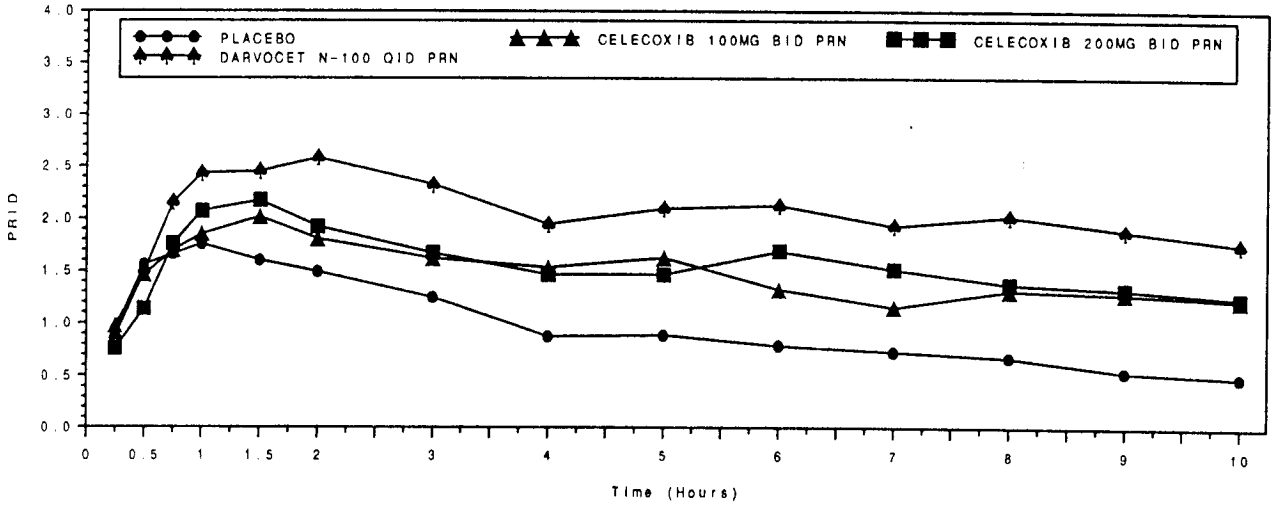
(a) Sample size is not extrapolated
(c) Model: PRID = mu + Ti + PI(0) + + Interaction term + center + error (b) Model: PRID = mu + Ti + PI(0)} + center + error
(e) Based on model (b) LSmeans, treatments with the same letter are not significantly different from each other. (d) Model: PRID = mu + Ti + PI(0)} + center + error + effect term +

DRAFT

CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 87
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - MULTIPLE DOSE - STUDY 028)

MEAN PRID SCORES OVER TIME



ASSESSMENT TIME POINTS (IN HOURS)

TREATMENT	4.00	5.00	6.00	7.00	8.00	9.00	10.00
DARVOCET N-100 QID PRN	1.95 (2.16) 40(a) A(e)	2.10 (2.25) 36 A	2.13 (2.27) 34 A	1.93 (2.11) 33 A	2.02 (2.16) 33 A	1.88 (2.16) 30 A	1.76 (1.98) 31 A
CELECOXIB 200MG BID PRN	1.47 (2.06) 28 AB	1.47 (2.09) 26 B	1.69 (2.30) 23 AB	1.52 (2.24) 20 AB	1.38 (2.22) 19 B	1.33 (2.11) 20 B	1.24 (2.00) 17 B
CELECOXIB 100MG BID PRN	1.53 (1.95) 37 AB	1.63 (1.87) 39 B	1.32 (1.97) 33 BC	1.15 (1.81) 28 BC	1.31 (1.93) 28 B	1.28 (2.00) 28 BC	1.22 (1.91) 25 B
PLACEBO	0.87 (1.58) 25 B	0.89 (1.48) 24 B	0.79 (1.60) 17 C	0.73 (1.56) 15 C	0.68 (1.55) 13 B	0.54 (1.38) 11 C	0.49 (1.43) 10 B
TREATMENT p-VALUE (b)	0.017	0.004	0.002	0.002	0.001	< 0.001	0.001
TRT*BASELINE p-VALUE (c)	0.253	0.689	0.739	0.752	0.737	0.848	0.700
TRT*CENTER p-VALUE (c)	0.055	0.035	0.009	< 0.001	0.035	0.181	0.244
GENDER p-VALUE (d)	0.566	0.416	0.563	0.863	0.471	0.912	0.687
BASELINE p-VALUE (b)	0.603	0.052	0.089	0.275	0.074	0.076	0.090
CENTER p-VALUE (b)	< 0.001	< 0.001	< 0.001	0.001	< 0.001	< 0.001	< 0.001
SURGERY TYPE p-VALUE (d)	0.662	0.174	0.337	0.336	0.427	0.538	0.686
RMS ERROR (b)	1.858	1.806	1.948	1.867	1.861	1.790	1.685

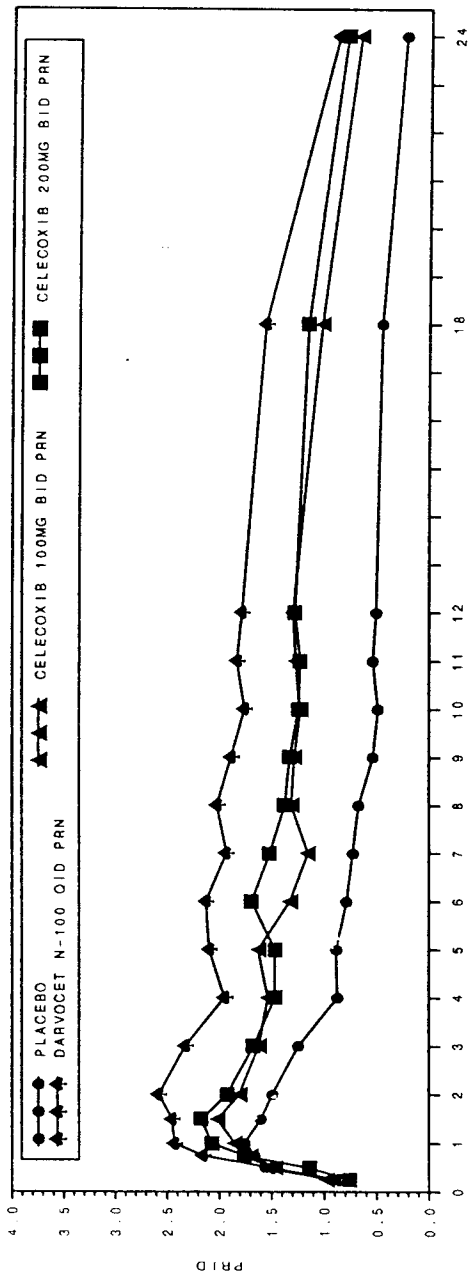
(a) Sample size is not extrapolated
(b) Model: PRID = mu + Ti + PI(0)j + center + error
(c) Model: PRID = mu + Ti + PI(0)j + interaction term + center + error
(d) Model: PRID = mu + Ti + PI(0)j + effect term + center + error
(e) Based on model (b) LSmeans. Treatments with the same letter are not significantly different from each other.

1 PRID28.SAS Friday, 15th May 1998 Page 3 of 3

CELECOXIB INTEGRATED SUMMARY OF EFFICACY - MANAGEMENT OF PAIN

TEXT TABLE 87
PAIN INTENSITY DIFFERENCE AND PAIN RELIEF (PRID, CATEGORICAL SCALE, EXTRAPOLATED) (CONTINUED)
MEANS, (STANDARD DEVIATIONS), SAMPLE SIZE WITHOUT EXTRAPOLATION AND FISHER'S PROTECTED LSD COMPARISONS (VERTICALLY)
(BOCF - MULTIPLE DOSE - STUDY 028)

MEAN PRID SCORES OVER TIME



TREATMENT	ASSESSMENT TIME POINTS (IN HOURS) 11.00	12.00	18.00	24.00
DARVOCET N-100 QID PRN	1.83 (2.15) 28(a) A(e)	1.78 (2.27) 29 A	1.56 (2.27) 21 A	0.87 (1.86) 14 A
CELECOXIB 200MG BID PRN	1.23 (2.05) 17 B	1.28 (2.12) 16 AB	1.15 (2.20) 11 AB	0.79 (1.68) 11 A
CELECOXIB 100MG BID PRN	1.27 (2.02) 23 B	1.30 (2.06) 20 AB	1.02 (1.90) 15 B	0.67 (1.45) 14 A
PLACEBO	0.54 (1.49) 8 B	0.51 (1.56) 7 B	0.46 (1.55) 4 B	0.24 (0.93) 4 A
TREATMENT p-VALUE (b)	0.002	0.004	0.012	0.127
TRT*BASELINE p-VALUE (c)	0.781	0.778	0.585	0.705
TRT*CENTER p-VALUE (c)	0.027	0.070	0.072	0.157
GENDER p-VALUE (d)	0.649	0.646	0.987	0.971
BASELINE p-VALUE (b)	0.068	0.103	0.154	0.133
CENTER p-VALUE (b)	< 0.001	< 0.001	< 0.001	< 0.001
SURGERY TYPE p-VALUE (d)	0.333	0.344	0.151	0.003
RMS ERROR (b)	1.821	1.908	1.833	1.457

(a) Sample size is not extrapolated
(c) Model: PRID = mu + Ti + Pi(j) + interaction term + center + error (b) Model: PRID = mu + Ti + Pi(j) + center + error
(d) Based on model (b) LSmeans treatments with the same center + error + effect term +
(e) letter are not significantly different from each other.

Time to Rescue Medication

Median times to rescue medication for the double-blind, post-oral surgery studies (Studies 025, 027, and 070) are presented in table 10. Celecoxib at doses of 50 mg SD, 100 mg SD, 200 mg SD, and 400 mg SD was associated with a statistically significantly longer duration of analgesic effect compared with placebo. The median time to rescue medication was longer with increasing doses of celecoxib; however, no statistically significant differences were present between the 100 mg SD, 200 mg SD, and 400 mg SD groups. Celecoxib at a dose of 25 mg SD did not separate from placebo. The 50 mg SD, although superior to placebo, had a median time to rescue medication under 2 hours.

Table 10: Median Time to Rescue Medication for Individual and Pooled Studies 025, 027, and 070 by Study and Treatment Group (hour:minutes)

Treatment Group	Study 025	Study 027	Study 070	Pooled
Placebo	1:17	1:20	1:06	1:15
Celecoxib 25 mg SD	1:32	---	---	---
Celecoxib 50 mg SD	1:48*	---	1:41*	1.51*
Celecoxib 100 mg SD	---	4:17*	2:36*	3:48*
Celecoxib 200 mg SD	3:05*	10:02*	4:15*	6:03*
Celecoxib 400 mg SD	---	---	8:13*	---

* Indicates statistical significance compared to placebo by log-rank test.

The results from the post-orthopedic surgery study (Study 028) supported the observation that the time to remedication or rescue medication is about 4 to 5 hours after a single dose of 100 mg or 200 mg of celecoxib. However, in this study, the time to rescue/remedication was longer for placebo (3 hours, 33 minutes) than seen in the post-oral surgery studies.

Time to Onset of Perceptible Pain Relief

Table 11 presents the Median Times to Onset of Perceptible Pain Relief for Studies 025, 027, and 070. All doses of celecoxib were numerically superior to placebo. Statistically significant differences were observed for celecoxib 50 mg SD (Study 025) and for 200 mg SD (Studies 025 and 027).

Table 11: Median Times to Onset of Perceptible Pain Relief for Studies 025, 027, 070 by Study and Treatment Group (hour:minutes)

Dose Levels	Study 025	Study 027	Study 070
Placebo	>24:00	00:58	>24:00
Celecoxib 25 mg SD	00:53	--	--
Celecoxib 50 mg SD	1:05*	--	00:42
Celecoxib 100 mg SD	--	00:45	00:39
Celecoxib 200 mg SD	00:38*	00:30*	00:44
Celecoxib 400 mg SD	--	--	00:43

* Indicates statistical significance compared to placebo by log-rank test.

Time to Onset of Perceptible Pain Relief was not measured in the post-orthopedic surgery study (Study 028) or the post-general surgery study (Study 029).

Pain Intensity Difference-VAS

Pain Intensity Difference-Visual Analog Scale (PID-VAS) was determined by asking the patients to rate their pain on a scale of 0 to 100 mm with 0 representing no pain and 100 representing worst pain.

In the double-blind post-oral surgery studies, celecoxib at doses of 100 mg (Studies 027 and 070), 200 mg (Studies 025, 027 and 070), and 400 mg (Study 070) showed statistically significantly greater improvement compared to placebo beginning by 1 hour postdose and continuing through 7-8 hours postdose.

The BOCF analysis for the single dose response in the post-orthopedic surgery study (#028) showed that celecoxib at doses of 100 mg SD and 200 mg SD was associated with numerically but not statistically significant greater mean PID-VAS scores compared with placebo from 1.5-8 hours postdose.

The mean PID-VAS scores after multiple dosing in the post-orthopedic surgery study (#028) showed that again, celecoxib 100 mg BID PRN or 200 mg BID PRN were numerically but not statistically significant superior to placebo beginning at about 1.5 hour and continuing through the entire 24 hour observation period. Using the BOCF method of imputation, celecoxib 200 mg BID PRN was significantly different from placebo at 7, 8 and 12 hours after the first dose of study medication. These findings however, cannot support the claim for the management of pain.

Sum of Pain Intensity and Pain Relief, Sum of Pain Relief, and Sum of Pain Intensity Difference for First 3, 6, 8, and 12 Hours

Sum of Pain Intensity and Pain Relief (SPRID) was calculated as the sum of the PRID scores for 3, 6, 8, and 12 hours for Studies 025, 027, 070, 028 (single and multiple dose).

Sum of Pain Relief (TOTPAR) was calculated as the sum of the PR scores for 3, 6, 8, and 12 hours for Studies 025, 027, 070, 028 (single and multiple dose).

Sum of Pain Intensity Difference (Categorical and VAS) (SPID and SPID (VAS)) were calculated as the sum of the Pain Intensity Difference Scores for 3, 6, 8, and 12 hours for Studies 025, 027, 070, 028 (single dose and multiple dose).

In Studies 025, 027, and 070, celecoxib at doses of 100 mg SD, 200 mg SD, and 400 mg SD showed statistically significantly greater improvement compared to placebo at 3, 6, 8 and 12 hours (BOCF analyses). The exception was in Study 027; the mean SPID score at 12 hours for the 100 mg SD was numerically but not statistically different from placebo.

In the post-orthopedic surgery study (Study 028), after a single dose of celecoxib 100 mg and 200 mg, mean SPRID, SPID and TOTPAR scores were numerically but not statistically significant greater than placebo at 3, 6, 8, and 12 hours. At 8 and 12 hours the mean SPRID and TOTPAR scores associated with celecoxib 200 mg were statistically greater than the corresponding measures associated with placebo.

In the multiple dose BOCF analyses, the mean SPRID, TOTPAR and SPID scores were numerically greater with celecoxib 100 mg BID PRN and 200 mg BID PRN compared to placebo but again, the differences did not reach significance. (According to LOCF analyses, celecoxib 200 mg BID PRN was statistically superior to placebo at 6, 8 and 12 hours for SPRID and TOTPAR).

Proportion of Patients and Time First Experienced at Least 50% Pain Relief
Following oral surgery (studies 025, 027, 070), the percentage of patients experiencing at least 50% pain relief during the study observation period was statistically significantly greater with celecoxib at doses of 50 mg SD, 100 mg SD, 200 mg SD, and 400 mg SD compared to placebo (table 12).

Table 12: Number (%) Patients Experiencing at Least 50% Pain Relief for Individual and Pooled Studies 025, 027, and 070 by Study and Treatment Group

Dose Levels	Study 025	Study 027	Study 070	Pooled
Placebo	9 (18%)	13 (24%)	7 (14%)	29 (19%)
Celecoxib 25 mg SD	21 (42%)	--	--	--
Celecoxib 50 mg SD	23 (46%)*	--	17 (49%)*	40 (47%)*
Celecoxib 100 mg SD	--	29 (53%)*	27 (54%)*	56 (53%)*
Celecoxib 200 mg SD	27 (54%)*	40 (71%)*	28 (56%)*	95 (61%)*
Celecoxib 400 mg SD	--	--	21 (60%)*	--

* Indicates statistical significance on Time to 50% Pain Relief compared to placebo using log-rank test.

In the post-orthopedic surgery study (Study 028) the percentage of patients who experienced at least 50% pain relief during the first 24 hours was determined. The analysis included patients who had received one or more doses of study medication. Over the 24 hours, 57%, 55% and 59% of the patients who received celecoxib 200 mg BID PRN, celecoxib 100 mg BID PRN and placebo, respectively, experienced at least 50% pain relief. It should be noted that the placebo response was much greater in the 028 trial than in other studies for all measures of analgesia efficacy.

Proportion of Patients and Time First Experienced 100% Pain Relief
One hundred percent pain relief was defined as a PR score of 4 (complete pain relief) and a PI (categorical) score of 0 (no pain).

Following oral surgery (studies 025, 027, 070), the percentage of patients experiencing 100% pain relief during the study observation period was statistically significantly greater with celecoxib at doses of 50 mg SD, 100 mg SD, 200 mg SD, and 400 mg SD compared to placebo (table 13).

Table 13: Number (%) Patients Experiencing 100% Pain Relief for Individual and Pooled Studies 025, 027, 070 by Study and Treatment Group

Dose Levels	Study 025	Study 027	Study 070	Pooled
Placebo	3 (6%)	9 (16%)	2 (4%)	14 (9%)
Celecoxib 25 mg SD	2 (4%)	--	--	---
Celecoxib 50 mg SD	7 (14%)*	--	4 (11%)*	11 (13%)*
Celecoxib 100 mg SD	--	15 (27%)*	14 (28%)*	29 (28%)*
Celecoxib 200 mg SD	14 (28%)*	21 (38%)*	11 (22%)*	46 (29%)*
Celecoxib 400 mg SD	--	--	12 (34%)*	---

- Indicates statistical significance on Time to First Experience 100% Pain Relief compared to placebo using log-rank test.

The proportion of patients experiencing 100% pain relief was not determined in the post-orthopedic surgery studies.

Summary and Conclusions

For the "general purpose" management of acute pain the usual requirement is (replicated) evidence of efficacy in at least two different type of pain models. One of which should be a model using multiple doses over several days in patients requiring short-term therapy.

During the development program of celecoxib, six studies were conducted to support the management of pain indication. Four single dose studies in the dental pain model (025, 027, 070, 005) and two multiple dose studies in the post orthopedic/general surgery model (028, 029,).

Of the four dental pain studies, three are considered to be pivotal (study 005 had a single blind design). In these studies, celecoxib at doses of 100 mg SD (Studies 027 and 070), 200 mg SD (Studies 025, 027 and 070), and 400 mg SD (Study 070) showed statistically significantly greater improvement in pain compared to placebo beginning at 1 hour postdose and continuing through nearly 8 hours postdose for the time specific efficacy measures. Time to Rescue Medication was statistically significant longer compared to placebo with celecoxib doses of 50 mg, 100 mg, 200 mg and 400 mg. Shorter Time to Perceptible Pain Relief compared to placebo was statistically significant for only the 200 mg dose (Studies 025 and 027). It is important to note that the NSAID comparators (ibuprofen 400mg and naproxen sodium 550mg) demonstrated a more rapid onset of analgesia and a statistically significantly greater peak response than celecoxib at all doses studied (25 mg, 50 mg , 100 mg, 200 mg, and 400 mg).

In the two multiple dose post general/orthopedic surgical pain studies interim analyses (not included in the protocol) were conducted. The reason given was that: "the enrollment had been slower than expected and the dropout rate had been higher than

expected, raising concerns that the model was not behaving as anticipated". Study 029 (post general surgery) was terminated because neither celecoxib nor the comparator (Darvocet-N) separated statistically from placebo. In the multiple dose post-orthopedic surgery trial (028) the only statistically significant differences favoring celecoxib over the placebo were at a dose of 200 mg for the pain relief plus pain intensity difference (PRID) measurement, at 6, 7, and 9 hours. Therefore, no substantial evidence has been demonstrated in the multiple dose post general/orthopedic surgical pain studies to support the management of pain indication.

A key issue here is whether a new molecular entity can gain a management of pain indication based only on evidence from single dose studies in one type of pain model. Although the results of the osteoarthritis studies lend some general support to idea that celecoxib can have an analgesic effect, the evidence of its utility for acute analgesic is weak; it "won" in three pivotal, single dose dental pain studies, but it appeared to be less effective than ibuprofen or naproxen sodium; and celecoxib failed in showing statistically significant efficacy in the treatment of pain in two multiple dose, 3-5 day post operative trials.

No outstanding safety issues have been demonstrated during the clinical trials conducted to investigate the treatment of pain. However, short-term studies are not expected to be a significant source for detecting adverse events of investigational new drugs.

Recommendations

1. This drug is recommended not approval for the treatment of pain at this time.
2. If additional multiple dose, 3-5 day studies show a statistically significant efficacy in the treatment of acute pain, the results of the currently submitted studies might serve as a supportive evidence.
3. If and when this drug is approved for the treatment of pain it is recommended that the labeling will reflect its performance relative to other NSAID's.

DRAFT

NDA 20998 – Celecoxib Safety Review

Reviewer: Maria Lourdes Villalba, MD
11/4/98

This NDA Integrated Safety Summary contains safety data from 51 studies, with a total enrollment of 18,439 subjects (13,072 individuals) of whom close to 9400 have received at least one dose of Celecoxib (Cx). With the exception of one continuing long-term open label study, the clinical studies included for analysis were completed by the end of April 1998. Two completed Japanese trials, ongoing trials and trials under other INDs are not included in the ISS analysis.

For the purpose of data presentation and analysis, the studies are grouped into the categories shown in Text Table 1 of the ISS: "**Phase I**" (single dose, multiple dose, drug interaction, hepatic impairment, and renal impairment), "**Arthritis**" (subcategorized as OA, RA, combined OA and RA, and long-term open label), and "**Analgesia**" (subcategorized as dental pain and surgical pain). I reviewed Phase I studies and the arthritis trials.

Text Table 1. Studies in Celecoxib Clinical Program Included in this Summary

Type of Study	No. of Studies	Study Numbers
Phase I		
Single dose	9	001, 006, 009, 018, 019, 037, 044, 084, 088
Multiple dose	11	003, 004, 010, 014, 015, 026, 032, 033, 043, 065, 069
Drug interaction	7	017, 038, 039, 040, 050, 051, 072
Hepatic impairment	1	016
Renal impairment	1	036
Arthritis		
OA		
Pivotal efficacy	5	020, 021, 054, 060, 087
Supportive	3	042, 013, 047
RA		
Pivotal efficacy	2	022, 023
Supportive	2	041, 012
OA/RA combined	2	062, 071
Long-term open label	1	024
Postsurgical analgesia		
Dental pain		
Pivotal efficacy	3	025, 027, 070
Supportive	1	005
Surgical pain		
Pivotal efficacy	1	028
Supportive	2	029, 080
Total	**51**	

Derived from Tables 1.1 through 1.5.

Dose and duration of exposure to Cx: Single dose studies were performed with doses ranging from 5mg p.o. to 1200 mg p.o. The highest doses used for multiple dose pharmacologic studies were up to 600 mg twice a day for 8 days. Chronic dosing in arthritis patients ranged from 100 mg BID to 400 mg bid for 24 months (2 ex-US combined OA/RA trials). Adverse experiences were monitored during study visits and by diary cards reviewed at each study visit. Adverse events included signs or symptoms, clinically significant laboratory abnormalities, or any abnormality detected during physical examination. All data on each adverse event were recorded onto a case report form along with the Investigator's opinion of intensity: mild, moderate and severe; seriousness (FDA definition) and relationship to study drug (none, uncertain, probable). Relationship to study drug was also evaluated by a Searle Medical Monitor. Terms used by the investigators to describe each adverse event were translated into the World Health Organization Adverse Reaction (WHOa.r.t.) terminology. In the arthritis studies, symptoms of arthritis of the type under study in a given trial were generally not considered as adverse events, except if they met the criteria for a serious event. Similarly, in the surgical analgesia studies, pain arising from the surgical procedure was not considered to be an adverse event. In the studies in which routine UGI endoscopies were performed, only symptomatic patients were considered to have had an adverse event, but all of the data related to the ulcer were included in the analyses of endoscopy findings.

Phase I trials –

Single dose studies:

Nine single dose studies involved a total of 312 healthy subjects (248 men, 64 women), ages 18 to 55, who received single oral doses of Cx of 5, 25, 50, 100, 200, 300, 400, 600, 800, 900 or 1200 mg. All studies were randomized. Seven studies were open label crossover studies, comparing different Cx doses or different Cx formulations; studies 001 and 009 were double-blind, placebo controlled; study 009 included ibuprofen as an active comparator. There were very few adverse events; there were no serious adverse events; two events causing withdrawal (mild toothache and appendictis following a single dose of Cx 200 mg, in study 084) were not considered to be related to study medication.

Two subjects in the 900 mg group (study 001), experienced elevation of liver enzymes. Laboratory values returned within the normal range within three to eight days of dosing for both of these subjects; additionally, laboratory values following re-challenge of the 900 mg dose in one of the subjects were all within the normal ranges.

Multiple Dose studies

Phase I Multiple Dose studies included a total of eleven studies. All studies were randomized; seven were DB, three open label and one single blind; seven studies were placebo-controlled and five were active comparator-controlled. In addition to clinical evaluation, laboratory and adverse events monitoring, Study 014 included endoscopic examinations. Most adverse events were mild or moderate in severity. There were no serious adverse events during these trials.

There were only four withdrawals due to adverse events. Two subjects (one in the Cx 40 mg and one in the Cx 200 mg), were withdrawn from study 003 due to abnormal labs (increased creatine kinase and increased SGOT, respectively). A young placebo subject with prepatellar bursitis was withdrew from study 015, ("Comparison of the SC-58635 PK profile in Elderly and Young subjects"). One patient with headaches withdrew from the ibuprofen arm in study 065.

Drug interaction studies - There were seven pharmacokinetic interaction studies: 017(with MTX in women with RA); 038 (with lithium carbonate in healthy adults); 039 (with glyburide in subjects with Type II Diabetes Mellitus), 040 (with warfarin), 050 (with diphenylhydantoin in healthy subjects), 051 (with tolbutamide in healthy subjects), 072 (with fluconazole and ketoconazole in healthy subjects).

[Of note, there were no formal interaction studies with ASPIRIN].

Two subjects in study 050 and five subjects in study 072 (3 in the fluconazole group and two in the ketoconazole group) had clinically relevant changes in hematocrit levels ($\geq$ 5%) at post-treatment. These changes were attributed to study-related phlebotomy.

Most adverse events were mild or moderate in severity. There was only one serious adverse event and it was not related to study drug (appendicitis in study 071). One subject withdrew from study 038 because of a urinary tract infection that required medication not permitted in the study. One placebo subject withdrew from the study 039 due to hypoglycemia. There were no deaths.

Clinical and laboratory data in patients with very high concentration of Celecoxib. The FDA PK team was concerned about possible adverse events among 6 patients who presented particularly high plasma concentrations of Celecoxib. Our review revealed no outstanding adverse events (Table), however safety laboratory studies were obtained after 48 hours and some transient effect could have been missed. Lab measurements were done at : Study 015: baseline, day 2, 4, 6, 8, 10, 12 and 14 post dose

065: baseline, day 4 and day 8 post dose

072: baseline and 3 weeks post dose

020: baseline, 2, 6 and 12 weeks post dose.

Table 2. Clinical manifestations and laboratory of patients with high celecoxib plasma concentrations.

Patient/ trial	Gender/ race/age	Celecoxib dose (mg)	Signs/ Symptoms	Hematology	Electrolytes	LFT's
221/015	73 C F	200 BID	Urticaria (d2) Diarrhea (d4) Sinusitis (d6)	Mild eosinophilia 10 % (n=0–3%) (d4)	↑ K: 5.1 (n=3.8-5.1) (d2 and d6)	Minimal ↑Alk phos :124 (n=23 – 120) (d6 and d10)
222/015	68 C F	200 BID	Intermittent dizziness	Mild eosinophilia 7% (d6)		
012/065	33 C M	600 BID		Minimal↑PT: 13.3(d4) and ↓ lymphocyte: 19% (n= 24%)		
031/072	33 C M	200 SD	Eye pain, peri orbital discomfort			
827/020	68 B F	100 BID				
461/020	80 B F	200 BID		↓ HTC: from 49% at baseline to 44% at 2 w and 40% at 6 w		

Hepatic Impairment. Study 016 was an open label, randomized, single and multiple dose PK evaluation study of Celecoxib in subjects with and without hepatic impairment in 12 mildly hepatically impaired subjects; 11 moderately hepatically impaired; and 25 normal subjects. Subjects were given one Cx 100 mg capsule on day 1 and 8, and one 100 mg capsule BID on days 4 to7. Most adverse events were mild and with the exception of two cases of diarrhea and one case of dyspepsia, were determined to be unrelated to the study drug. There were no withdrawals and no deaths. No significant laboratory changes.

Renal Impairment. Study 036 was a randomized, DB, PC and AC, parallel study of **75 subjects** (36 men, 39 women) ages 39 to 81, with stable chronic renal insufficiency, who received **SC 200 mg BID,** naproxen 500 mg BID for **seven days,** or placebo on days 1 to 6 and a single morning dose on day 7. There were no serious adverse events and no deaths. Two withdrawals in the placebo group (one headache, one confusion) were not considered to be related to study drug.

[In summary, from the phase I studies, Celecoxib appears to have an acceptable safety profile at doses explored . Most adverse events were mild or moderate, there were a few withdrawals and serious adverse events, most of them probably unrelated to the drug, and there were no deaths. Two patients presented reversible elevation of LFT's after a single dose of Cx, 900 mg.

Six patients who showed very high Cx plasma concentrations, had not particularly worrisome clinical or laboratory adverse event.

Regarding the 7 patients who showed clinically significant drop in hematocrit in study 050 and 072, it is not completely clear to me whether it was just due to repeated flebotomy or if there is another explanation. In this study fluconazole and ketoconazole significantly affected Cx metabolism.

In study 016, 23 patients with hepatic impairment received Cx 100 mg BID for 4 days. Hepatic impairment resulted in an increased mean trough concentration with greater hepatic impairment associated with increased mean trough plasma concentrations. Celecoxib was well tolerated without significant changes in LFT's. Does it mean that patients will similarly tolerate 200 mg BID for longer periods? Does this justify the "no need for dose adjustment" in patients with mild to moderate hepatic impairment? Additionally, patients with severe impairment were not studied.

In study 036, 40 patients with stable chronic renal insufficiency tolerated Cx 200 mg BID for 7 days. Again, this is a short period and Cx should be used with caution in patients with renal disease].

Arthritis trials – O.A, R.A and combined trials.

Osteoarthritis trials (eight trials: 020, 021, 054, 013, 042, 047, 060, 087)

Two to six-week OA studies.

There were five randomized, double blind, multi-center, parallel studies, that compared different doses of Celecoxib (ranging from 25 mg BID to 400 mg BID for 4 weeks and 200 QD for 6 weeks) to placebo, in patients with OA of the knee in a flare state (013, 047, 060, 087), or to an active comparator (diclofenac 50 mg BID) in patients with OA of the hip or knee of more than 6 months (study 042). 2787 patients were randomized (843 men, 1944 women); 2479 Caucasian, 218 Black, 61 Hispanic, 11 Asian, 18 Other. 2778 patients actually received at least one dose of study drug.

Table 3. Randomization in two to six-week OA studies

Treatment	Study 013 (2 weeks)	Study 042 (6 weeks)	Study 047 (4 weeks)	Study 060 (6 weeks)	Study 087 (6 weeks)
Placebo	71		101	232	244
Cx 25 or 40 mg bid	73		101		
Cx 100 mg bid or 200 mg q.d.	76	347	101	454	474
Cx 200 mg bid	76				
Cx 400 mg bid			99		
Diclofen 50 mg bid		341			
total	293	688	402	686	718

Table 4. Two to six week OA trials. Adverse events requiring withdrawal and serious adverse events, (013 (2w), 047(4w), 042, 060, 087(6w)). S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients	Placebo N= **648**	SC 25 or 40 mg BID N=**174**	SC 100 mg BID or 200 QD N=**1452**	SC 200 mg BID N=**76**	SC 400 mg BID N=**99**	Diclofenac 50 mg BID N=**341**
Dyspepsia	1		2		1	1
Diarrhea	2		3		1	5
Abdominal Pain	6	1	5			7
Nausea/vomiting	4		9			2
Esophagitis/gastritis						1
G.I. bleeding		1 N S (rec)				
Abdominal fullnes, nausea			1			
Palpitations			2 (one arr S N,)	1 (arr) SN		
CHF			1 S N			
Chest pain, CAD	1 (MI) S N	1 N,	1 S, 1 S N, DEATH			
Headache	1		1 N			1
Dizziness	2		3 N,			
Hyperesthesia, numbness, tingling	1		2 N			
Anxiety/irritabilit	1		1			
Insomnia			1			
Rash/urticaria/ allergic reaction	4 (one S)	1	11	1	2	1
Skin lesion			1			
Pruritus	1			1	2	
Back pain			2 N			
Arthralgia/myalgia	1 1 N				1	
Peripheral pain	1 N	1 N	2 N.			1 N
Accidental injury	2 N,		1 N S			1
Malignancy	2 S N,					
Hematuria						1 N
Fatigue	1					1
Dyspnea			1 N			
Respiratory inf: URI, bronchitis pneumonia,	1 N		2 N			1
Broncospasm		1	1 S			
Phlebitis						1 N
Weight gain			1			
Alopecia			1 N			
Hemol uremic S.					1 S N	
Edema	1 (face)		2			1
Renal insuff	1 N					
Septic arthritis			1 S N			
Herpes Zoster			1 S N			
Stomatitis			1 N			
Dry mouth	1 N					
Tox due to Non study drug	1 S					

Hyperglycemia			1 S			
Elevated CPK	2 N		1 N			
Elevated SGOT/SGPT						3
Decreased WBC						1
Hyperkalemia					1	
Anemia			1			

Serious events with no withdrawal:

Trial 013: none
Trial 042: Diclofenac: 1 angina N, 1 shceduled TKR N
Trial 047: Placebo 1 Lung Ca N,
Celecoxib 25 bid – 1 rectal hemorrhage N,
Cx 100 bid – 1 chest pain and bronchospasm N
Trial 060: Placebo Urinary incontinence N
Cx 100 bid – 1 CHF N, 1 CVA N
Trial 087: Cx 200 QD – 1 basal cell Ca, N.

12 week OA trials

Included three double-blind, placebo-controlled and active-controlled, multicenter (U.S. and Canada), parallel studies with a total of 3268 patients, ages 19 to 93, with OA of the knee (020 and 021) or hip (054) in a flare state, randomized to receive SC-58635 50 mg capsules BID (671), 100 mg BID (644) or 200 mg BID(1114); Naproxen 500 mg BID; or placebo, for 12 weeks. Adverse events requiring withdrawal are shown in Tables 020, 021 and 054. There was only one serious event considered to be related to the study drug (patient in study 054 with abdominal pain and possible ileus). There were no deaths.

Table 5. Randomization in 12-week OA studies:

	Study 020	Study 021	Study 054	Total
Placebo (n)	204	242	218	664
Celecoxib 50 bid	203	252	216	671
Celecoxib 100 bid	197	240	207	644
Celecoxib 200 bid	202	233	213	648
Naproxen	198	226	207	631

Table 6. Adverse events requiring withdrawal, study 020, 021, 054 .

S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients	Placebo N=**664**	SC 50 mg BID N=**667**	SC 100 mg BID N=**644**	SC 200 mg BID N=**648**	Naproxen 500 mg BID N=**631**
Dyspepsia	6	6	10	9	16
Diarrhea	2	5	4	3	3
Abdominal Pain	2	8	5 (+ one pt with abd abcess, N)	9	18
Nausea/vomiting	6	3	4	2	8
Obstruction	1 (intest gangrena) SN	1 small bowel S N	1 small bowel S N		
Upper G.I. bleeding	1		1 (gastric ulcer)		5 one S
Abdominal fullnes, flatulence			1	1	2
Pancreatitis			1 S N		
Stomatitis		0136 N			
Rectal burning			1		
Palpitations/arrhyt	1 A.fib N,	2 (one SVT SN)	2		1
CAD	1		1 S N	3 S N	1 S N
CHF				1 S N	
HTN/aggr HTN			1	4 (one S, two N)	
Headache	2	3	3 (2 N)	1	1
Dizziness	1	1	3	2	1
Tinnitus			1	2 N	
Depression/ somnolence			2 N	1	2
Anxiety/irritability/ insomnia		1	3	2	
Abnormal gait				1 N	
Hypersthesia/numb			1		
CVA	1	1 N	2 N	1 (w/ HTN)	
Rash/urticaria/allergic reaction	1	9	7 (one had swollen lips)	14	8
Pruritus	1		2	1	
Bronchospasm	1	1 N			
Skin lesion			0284 N dermatitis)		
Herpes Zoster			0857 N		
Arthralgia/myalgia	2	1	2 N	1 N	
Back pain	4	1	3 N	2 N	1
Peripheral pain			1 N	1 N	
Accidental injury	2	1 N	2 S N		3 N
Miscellaneous rheum. complaints	1	1 SN	2 N (one gout attack)	1	
Malignancy	2	1 S N	3 S N	1 S N	2 S N
Fatigue	1		1	2 N	
Dyspnea	1				
Pulm embolism				1 S N	2 S N
URI/Bronchitis/ pneumonia	1 N	1 N		2 N (one S pneumonia)	
Edema	1		2 N (one face ede)		
Flebitis		1 N			
Miscell.		1 goiter N		1 temp arteritis	1 fibroids, 1 ecchym, 1 hyperglyc
Elevated CPK			1 N		
Elev. Creatinine		1+ proteinuria and peripheral edema		1	
↑ SGOT/SGPT	1		1		

Anemia		1	1 + proteinuria and thrombocytemia		3
Leukopenia	1 N				

RA trials **Rheumatoid Arthritis Trials** (022, 023, 041, 012).

The RA trials were multicenter, randomized, double blind, parallel studies involving a total of 3237 patients (863 men, 2374 women), ages 20 to 90, (2828 Caucasian, 208 Black, 161 Hispanic, 19 Asian , 21 other) with RA in a flare state (012, 022 and 023) or with stable RA (041), who received Celecoxib ranging from 40 mg BID for four weeks up to 400 mg BID for 12 weeks and 200 mg BID for 24 weeks.

Table 7. Randomization in RA trials

Treatment	Study 012 (4 weeks)	Study 022 and 023* (12 weeks)	Study 041** (24 weeks)
Placebo	85	452	
Cx 40 mg bid	81		
Cx 100 mg bid		468	
Cx 200 mg bid	82	453	326
Cx 400 mg bid	82	434	
Naprox 500 mg bid		443	
Diclofenac SR 75 mg bid			329
total	330	2250	655

*Studies 022 and 023 had similar design. Study 022 specifically evaluated UGI safety and involved patients with no significant lesions on endoscopy. ** Study 041 was an ex-US study (Australia, Europe, South Africa, New Zealand and Israel) evaluate that also particularly evaluated GI safety.

Table 8. RA trials. Adverse events requiring withdrawal and serious adverse events, (012 (4 w), 022, 023 (12 w), 41(24 w)) **S** = Serious event. **N** = found to be not related to study drug by Searle Medical Monitor.

Total number of patients	Placebo **N=537**	40 mg BID N=**81**	SC 100 mg BID **N=468**	SC 200 mg BID N=**862**	SC 400 mg BID **N=951**	Naproxen 500 BID N= **443** , or Diclofenac 75 mg BID (*D*) N=**329**
Dyspepsia	2	1	3	5	5	6 (one S)+ *8 D*
Diarrhea	1		1	6	2	*5 + 5 D*
Abdominal Pain	2		4	10	1	*7 + 27 D*
Nausea/vomiting	1			5	1	*1 + 3 D*
Esophagitis/gastritis				1		
Rectal burning						
S.Bowel obstruct						*1 D* N
G.I. bleeding/ ulcer				1		*6 D (one S)*
Abdominal fullnes, flatulence					1	*2 D*
Palpitations				1 N	2	
SVT						
CHF				1 N		
Chest pain, CAD	1 SN, 1(MI),SN		2 S (one MI, N)	1 S N		1 N
Headache	3			2	1	*1 D*
Dizziness				1+ headac & face edema	1	*2 + 2 D*
Tinnitus	1		1 (+ otitis med & periorb edema)		2	1
Hyperesthesia, numbness, tingling				0428/22 N		
Depression/somnolence	1			0333/23,		*1 + 1 D* S
Anxiety/irritabilit			1			*1 D*
CVA				0598/41 SN		1 SN
Rash/urticaria/allergic reaction	6 + 1 (+ face edema & broncosp)		4	**16** (one w/ periorb edema, one w/ face edema, one w/ **angioedema)**	**12** (one w/ swollen face and **laringeal edema**, one w/ face edema, one w/ sob, two w/ numbness & paresthesias, one w/ rigors & chills, one w/ **anaphylactoid react** N),	3 + *1 D*
Pruritus			3			
Bronchospasm	1					
Skin disorder				**2 skin ulceration** N, **1 fingertip excoriations** N.	**1 skin ulcer** (diabetic ulcer), **1 vasculitic lesions** both hands 1 contact dermatitis	
Accidental injury					1 SN	
Malignancy			1 SN	2 S N (one DEATH)	1 SN	
Fatigue			1	2		
Dyspnea				1		
Pulm embolism						*1 D* SN
Respiratory inf: URI, bronchitis pneumonia,	1			3 N		

Phlebitis						*2 D* N
Edema	face 1			1 Face & mouth	1 periph	1
Leg cramps			1	1		
Hematuria						
Kidney stone	1 SN					
Stomatitis				1		
Miscell.					1 epistaxis	*1 D* S N (recto vesical fistula)

Elev. BUN/creatinine				0519/41		*2 D*
Elevated SGOT/SGPT			0288/22	0915/23		
Hipokalemia			0663/23			
Anemia				0785/22 N (+ thrombocytemia		*1 D* S

Serious Adverse Events without withdrawal:

Trial 012: none

Trial 023:
0501 Myocardial Infarction , SC 200 bid (N)
0757 Basal skin cell ca. Naproxen
0485 Accidental injury, diabetic, gangrenous toe (SC 200 bid) (N)
One patient with colon CA in SC 100 bid
1137 Cholecystitis on placebo

Additional adverse event of note in trial 023: # 0895 (neuropathy, syncope (N), fungal infection ringworm)

Trial 022:
Placebo: 0558 chest pain , 2 skin malignancy N
Naproxen 500 mg bid: 0042 facial cellulitis , aggravated RA 1 patient
Celecoxib: 0921 upper resp. infection. N. SC 100 bid,
0462 pneumonia N SC 200 bid, 1625 bronchitis N SC 200 bid
0921 upper resp. infection. N. SC 100 bid,
0212 angina pectoris – SC 400 bid,
0683 aggravated HTN (N) SC 400 bid

Trial 041:
Diclofenac 75 mg bid: 1 back pain, 1 lymphangitis, 1 gastroenteritis,1 CTS release, 1 amputation of little toe,
1 cellulitis. 1 pyometra,
Celecoxib 200mg bid: 0790 Septic arthritis (post op) "shoulder sepsis" S N.
0126 Myocardial Infarction. S N, 0039 depression S N,
0707 dyspnea, 0202 and 0093 pneumonia S N,
0481 , 0892 and 0157 accidental injury S N.
0011 anemia + pleural eff

COMBINED OA AND RA.

Table 9. Adverse events requiring withdrawal and serious adverse events (062 and 071 (24 weeks, ex US)) S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients		Cx 200 mg BID N = **636**	Ibuprofen 800 mg TID N = **346**	Diclofenac 75 mg BID N = **387**	Naproxen 500 bid N = **267**
Dyspepsia		2	3	11	2
Diarrhea		1		4	
Abdominal Pain		3	7	8 (one N)	6
Nausea/vomiting		4	5	2	2
Constipation				1	
Esophagitis/gastritis/ gerd		2		2	3
S.Bowel obstruct					1 S
G.I. bleeding/ gastric ,duodenal, esoph ulceration		2 S (one intestinal perforation N),	7	7 (two N)	5
Abdominal fullnes, flatulence			1	1	
Palpitations		1/71		1	1S (arr).
SVT					1 S N
CHF		1/71			
Chest pain, CAD		**3/62 S N**	1/71 MI S N	1/62 S N	1 MI. S N
Syncope/ sudden death		1/71	1/71 sudden **DEATH, S N**		
Hypertension		1 S		1 N, 1 **DEATH** , S N	1 N
Hypotension			1 hypoten		
Dizziness			3/71		1
Tinnitus/deafness		1			
Hyperesthesia, numbness, tingling				2 (one N)	
Depression/somnolence			1/71	1	
Abnormal gait/ dystonia		1			
CVA					1 **DEATH** (brain stem infarct) S N
Rash/urticaria/allergic reaction Skin disorder		2 (one N)	2/71	2 (one **anaph shock)** 1 soft tissue infection N	3
Arthralgia/myalgia/ worsening arthritis					1
Accidental injury		2		1 S N	
Malignancy		1 S N.		1 S N	
Dyspnea		**1**	1	1 COPD exac S N	1 N
Respiratory inf: URI, bronchitis pneumonia,		2 (one otitis media + deafness) N		1 S N	
Cough			1		
Pleural eff					**1/71 S N (empyema D)**
Edema			Face 1/71	Face 2/71	Face 1/62.
Miscell		1 S N (kidney stone)		1 Breast enlargement	

Urinary infection		1 N			1 S N

Elev. BUN/creatinine			1		1
Abnormal liver, ↑SGOT/SGPT		1			3
Anemia			3		1

Serious AE without withdrawal:

Trial 062:
Naproxen: 2 dyspnea, 1 SVT, 1 intestinal obstruction
Celecoxib 200 bid: 1 psychotic episode N, 1 aggravated hypertensionN, 1 pleural effusion N

Trial 071

Ibuprofen 800 mg TID: 1 pyelonephritis, 1 emergent surgery
Diclofenac 75 mg BID: 1 Angina pectoris, 1 Copd exacerbation, 1 atrial flutter, 1 scheduled surgery
Celecoxib 200 mg bid: 1 urinary infection N, 1 basal cell ca N, 1 depression aggravated, 1 scheduled surgery, 1 emergent surgery.

Data analysis

After an initial safety review of all the controlled arthritis trials, statistical comparison of the number of selected serious adverse events and adverse events causing withdrawal for Celecoxib (50 to 400 mg BID doses), placebo and active comparators, was requested to Searle on 10/28/98 and provided to FDA on 11/2/98.

All OA, RA and combined OA/RA trials were divided in two groups:
a) < 12 weeks duration (012, 013, 042, 047, 060, 087)
b) ≥ 12 weeks duration (020, 021, 022, 023, 041, 054, 062, 071)

We requested the following categories:

I - Gastrointestinal
a) Hard GI endpoints (perforation, obstruction, UGI bleeding)
b) Dyspepsia
c) Abdominal pain
d) Nausea

II - Cardiovascular:
a) Palpitations, arrhythmia
b) Congestive heart failure
c) Angina/ coronary artery disease/ cardiac chest pain
d) Hypertension/ aggravated hypertension

III – Skin
a) rash, urticaria, allergic skin reaction, dermatitis
b) skin ulceration/skin lesion (exclude skin malignancies)

IV – Allergic reaction (excluding skin rash)/ anaphylactoid reaction/ anaphylactic shock, bronchospasm/ asthma/ angioedema

V – Infections
a) respiratory (otitis, rhinitis, pharyngitis, upper respiratory, sinusitis, bronchitis, pneumonia)
b) urinary (cystitis, bladder, kidney, pyelonephritis)
c) sepsis
d) septic arthritis, joint infection
e) skin infection, herpes zoster

Summary of the analysis performed by Searle, based on Searle's database (need to fill out the numbers) (my numbers may look different because some patients withdrew with more than one event and I chose only one, may be different from the one chosen by Searle):

Gastrointestinal adverse events: For >= 12 week trials.

For major GI events: (Perforation, Ulcers and Upper GI Bleeding) serious and causing withdrawal, there was a statistically significant difference in favor of Celecoxib when compared to active comparators. There was no difference between active comparators and placebo.

For dyspepsia and abdominal pain requiring withdrawal, there was a significant difference between active comparators and Cx and active comparators and placebo.

For <12 week trials: The incidence of dyspepsia, nausea and abdominal pain severe enough to require withdrawal was neither different to placebo nor to the active comparators.

[Celecoxib a the doses proposed (100 and 200 mg BID) seems to have a safety profile superior to other NSAIDs regarding the incidence of major GI complications. Of note, there were "minor" GI side effects, still bad enough to require withdrawal in 1 to 3% of patients] [Again, these data comes from Searle's database; Dr. Goldkin , the Gi reviewer has different data].

Of note, there was no significant number of patients withdrawn due to elevated liver function test and this analysis was not requested to the company. However, it may be worth it to look at LFT's in patients withdrawn due to other GI adverse events]

Cardiovascular events:
Among the ≥ 12 week trials there were 16 CAD related events among patients on Celecoxib (0.4%), 5 among active controls (0.2%) and 6 among placebo (0.5 %). The differences were not statistically significant. The incidence of arrhythmia was < 0.1 % for all groups.

<12 week trials, the incidence of CAD related events and for arrhythmia was 0.1 % or less for all groups.

Skin ulceration– In the November 2 Searle's database there was only one case of skin ulcer in a placebo <12 w patient. Among the skin lesions causing withdrawal there was 1 in Cx 200mg bid in the ≥ 12 w trial's (one case of a patient with a diabetic ulcer and a gangrenous toe).

[Additionally I found 3 cases of Skin Ulceration, 1 case of skin vasculitis, 1 case of "excoriation of the fingertips", 1 case of "contact dermatitis". The nature of these skin lesions is not clear to me. Were they allergic, infectious, ischemic? There were also at least 2 cases of nasal septum ulceration among RA patients reported as non serious and no requiring withdrawal.
Of note, unexplained skin lesions have been observed in dogs at higher doses, not used in humans with celecoxib and with other COX 2 inhibitors].

Allergy - There was a high incidence of different kind of skin rashes. I think that these rashes were mostly allergic and should alert us to the possibility of more severe allergic reactions.

[The pathophysiologic mechanism responsible for NSAID-induced allergy is not known. It is thought to depend on inhibition of cycloxigenase (COX 1, 2 or both?) coupled with upregulation of 5-lipoxigenase dependent pathways.

Two cases of bronchospasm were seen among placebo. No major allergic reactions were seen in the active comparator group. However there were cases of angioedema, laryngeal edema, bronchospasm, and anaphylactoid reaction (1 each) among Celecoxib patients. These trials were not powered to detect infrequent adverse events particularly among the active comparators. Additionally these trials excluded patients with known allergy to NSAID and sulfa drugs.

Celecoxib should be used with caution in people with known allergy to other NSAIDs and sulfa drugs].

Incidence of serious infections – There were no statistically significant differences in the number of serious events or infections requiring withdrawal among the Cx compared to placebo and active comparators.

Renal – Regarding renal adverse events and laboratory, Celecoxib has a safety profile comparable to a mild NSAID. The significance of the mild increase in chloride among Celecoxib patients, particularly without bicarbonate data is difficult to

interpret. The three special renal studies were underpowered to detect infrequent serious adverse events; even active comparators appeared to be benign to the kidney.

APPEARS THIS WAY
ON ORIGINAL

DRAFT

Division of Gastrointestinal and Coagulation Drug Products
Medical Officer's Consult Review

NDA:	20-998
SPONSOR:	G.D. Searle & Co.
REQUESTED BY:	Division of Anti-Inflammatory, Analgesic and Ophthalmalogic Drug Products: HFD-550
DATE OF REQUEST:	July 13, 1998
DRUG:	Celecoxib (Celebra) capsules 100 and 200 mg. Oral BID
Pharmacological category:	Selective cyclooxygenase –2 inhibitor
PROPOSED INDICATION:	For the acute and chronic use in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis and for the management of pain
MATERIALS REVIEWED:	Background literature on nonsteroidal anti-inflammatory drugs (NSAIDs) and gastrointestinal toxicity. Published articles on meloxicam, a selective Cox II inhibitor marketed overseas G.D. Searle &Co. studies Pivotal studies sponsored by G.D.Searle and Co. regarding gastroduodenal safety based on upper gastrointestinal endoscopy: 021,022,041,062,071 reviewed in detail. This assessment included validation of endoscopic coding.
CONSULTANT:	Lawrence Goldkind M.D.

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Executive Summary

The object of this consult is celecoxib (Celebrex™) a selective inhibitor of cyclooxygenase-2. This form of cyclooxygenase inhibitor has been developed in the hopes of minimizing the gastrointestinal and renal toxicity associated with the nonselective or less selective cyclooxygenase inhibitors currently available for the treatment of pain and inflammatory diseases. The latter category of relatively nonselective cyclooxygenase inhibitor drugs is generically known as non-steroidal antiinflammatory drugs (NSAIDs). The sponsor claims in the Integrated Summary of Safety Information that celecoxib is distinctly different in safety profile. Specifically, "it is associated with a lower rate of gastroduodenal ulceration and significantly fewer clinically significant upper gastrointestinal (UGI) events than NSAIDs and incidence rates of these events and ulcers are similar to placebo." The sponsor's definition of such events is found within this review. This review will assess these claims as reflected in the endoscopic studies 021, 022, 041, 062 and 071.

In this review results of the five pivotal studies related to endoscopic evidence of UGI toxicity have been examined. Development of gastroduodenal lesions, defined by ulcers and erosions identified endoscopically, has been chosen as the primary endpoint. Although a valid endpoint of interest, gastroduodenal lesions cannot be accepted as an adequate surrogate for clinically significant UGI events. The very definition of clinically significant UGI events is not standardized. There are no adequate data on the extent of correlation between upper g.i. lesions and clinically significant UGI events to warrant "surrogacy". Theories on gastric mucosal adaption to cyclooxygenase inhibition and pre-clinical evidence that cyclooxygenase 2 may be beneficial for ulcer healing, further complicate the relationship between ulcer formation and progression to clinically significant events. General references to clinically significant UGI events and comparisons to placebo are made throughout the sponsor's submission. These two issues however are not defined in the studies in a way to prospectively or statistically evaluate these claims.

The sponsor has provided reproducible and robust statistically significant evidence in three studies that celecoxib at the doses proposed (200 mg b.i.d.) is associated with less gastroduodenal lesions than the recommended dose of naproxen, 500 mg b.i.d. there was no consistent dose-related increase in ulcer rate at 100, 200 or 400 mg b.i.d. regimens of celecoxib. The relative risk for gastroduodenal ulcers associated with naproxen use compared to celecoxib ranged from 2.7 to 9.

Results of a single study were submitted comparing gastroduodenal lesions associated with celecoxib (b(4)) or ibuprofen, at the recommended dose of 800 mg b.i.d. This study revealed a robust statistically significant advantage of celecoxib over ibuprofen. The relative risk of ibuprofen compared to celecoxib in this study was 3.3.

Two studies (b(4)) comparing celecoxib [b(4)] and diclofenac 75 mg b.i.d. revealed inconsistent results regarding the superiority of celecoxib in regards to gastroduodenal injury.

I. Background and Introduction

NSAID induced gastrointestinal side effects are the most frequently reported adverse drug related events in the United States. Although most of these are minor, serious adverse events such as perforation and bleeding are reported to occur in 2-4% of patients on chronic therapy. Use of this category of drugs is associated with gastrointestinal adverse events from the esophagus down to the colon and rectum. The most clinically relevant adverse events occur in the stomach and duodenum in the form of ulcers, which can result in complications such as bleeding and perforation, although asymptomatic erosions and ulceration are not uncommon (and according to some studies occur in up to 20% of rheumatologic patients on chronic NSAID therapy). NSAID related ulcers tend to cause fewer symptoms than other forms of ulcer disease and therefore may more commonly present with complications rather than dyspeptic symptoms. The broad based usage of NSAIDs for acute and chronic pain in the general population as well as in the large population of arthritis patients translates into a large absolute number of serious complications. It has been estimated that at least 2600 deaths and 20,000 hospitalizations per year in the United State scan be attributed to NSAID use in rheumatoid arthritis patients alone[1]. Put another way, the chance of hospitalization or death from a gastrointestinal adverse event is 1.3-1.6% per year in patients with rheumatoid arthritis. Some authors estimate over 7000 deaths per year is attributable at least in part to the use of NSAIDs in the general population in the U.S. alone. Estimates from the United Kingdom suggest 1200 patients a year die there as a result of NSAID adverse events[2].

NSAID gastroduodenal injury is multifactorial. The most commonly cited pathogenic mechanism is the inhibition of cyclooxygenase (Cox) and its catalytic effect on arachadonic acid and prostaglandin G2 locally in gastroduodenal mucosa and the subsequent depletion of endogenous constitutive prostaglandins. This appears to be the major mechanism of gastroduodenal injury. Mucosal mucus layer penetration of unionized drug in the acidic gastric environment and subsequent mucosal epithelial cell damage is another mechanisms of NSAID gastroduodenal injury. Important clinical support for the Cox inhibition mediated mechanism comes from seminal studies involving misoprostol (a synthetic analog of prostaglandin E1 available in the U.S. as Cytotec). At adequate doses and regimens this drug significantly reduces both overall ulcer formation and more importantly, ulcer complication rates. Gastric ulcer rates in NSAID treated patients on misoprostol were 4% compared to almost 16% in placebo treated patients. [3] In another study serious complications such as bleeding, perforation and gastric outlet obstruction were decreased by 40% in misoprostol treated rheumatoid arthritis patients on NSAIDs[4]. This placebo controlled study required nearly 9000 patients to show statistical significance due to the low overall occurrence of these adverse outcomes in placebo treated patients (1.5% per year). An important result of the large well controlled studies of misoprostol was the risk stratification for ulcers. Advancing age, cardiovascular disease, a history of ulcer disease and especially a history of complicated ulcer disease are risk factors for NSAID related ulcers. An earlier population based retrospective case-control study from the United Kingdom had found increasing age, gender, prior peptic disease, alcohol consumption, smoking, anticoagulant usage and corticosteroid usage to be risk factors for peptic ulcer complications. Other studies have yielded contradictory results, especially related to tobacco and corticosteroid usage. Most studies however are weakened by small size, as well as retrospective and uncontrolled approaches.

There is no conclusive evidence that the occurrence of NSAID related ulcers will predict the risk of complicated ulcers. This intuitive assumption, however is accepted by many and certainly no better surrogate exists for the more clinically relevant endpoints of bleeding, perforation, obstruction and death. Important evidence supporting this assumption is the cross study analysis of two studies involving misoprostol that revealed a risk reduction of 40-50% in both ulcer risk and complicated ulcer risk.

Historically, the concept of multiple forms of Cox dates back to 1972 based on observations that acetaminophen blocked prostaglandin synthesis in the central nervous system but not in peripheral tissues. In 1980 studies showed that prostaglandin synthesis could be inhibited by sodium salicylate at sites of inflammation without affecting gastric prostaglandin synthesis. In 1991 the existence of multiple isoforms of Cox was proven through molecular characterization of a second form. This discovery has led to a flurry of theories, models and studies of the physiologic and pathophysiologic roles of the different forms as well as attempts to capitalize on the different tissue locations of the two isoforms to tailor therapy that requires

inhibition of Cox. Cyclooxygenase-1 (Cox-1) is a constitutive enzyme that has been described as having a "housekeeping" role in maintaining the integrity of the gastric mucosa and renal function while Cox-2, which is more inducible, is found in association with inflammatory processes. The location on different chromosomes would support distinctly different roles for these two isoforms. Crossover in tissue location of the two forms does exist (except in platelets), and messenger RNA for both forms has been found in most human tissues tested including stomach, small intestine mammary gland, uterus, pancreas, liver, kidney, brain, thymus, prostate and lung. There is, however, an impressive differential distribution of each isoform in specific tissues. In general Cox-1 is prevalent in stomach, kidney and platelet while Cox-2 is prevalent at sites of active inflammation.

An array of selective Cox-2 inhibitors has been developed and extensively tested. Meloxicam, an anti-inflammatory drug, is just such a Cox-2 selective inhibitor and has been extensively tested and marketed in Europe . While clearly displaying the anticipated decrease in GI toxicity at lower dosage regimens, it has not been free of associated adverse events. Early trials with 30-60 mg. daily dosing schedules revealed similar incidence of adverse events compared to standard NSAIDs . Even clinically accepted doses of 15 mg a day revealed some GI toxicity, although less than active comparators of piroxicam and diclofenac. Clearly issues of degree of specificity, dose, relative efficacy and safety all must be addressed when assessing the safety and efficacy of these compounds. Assays for Cox isoform specificity are not well standardized. There are multiple in vivo and in vitro assays with much discrepancy among the various assay methods. The relative merits of these drugs and their safety and efficacy profiles therefore cannot be accepted without critical clinical scrutiny.

Celecoxib is the subject of NDA 20-998. It is a selective Cox-2 inhibitor. The GI consultation is specifically requested to review GI safety claims related to this drug based on pivotal endoscopic studies. The Integrated Summary of Safety Information includes claims that celecoxib is associated with a lower rates of gastroduodenal ulceration and significantly fewer clinically significant UGI events than NSAIDs, as well as incidence rates of these events and ulcers that are similar to placebo.

II. Scope of Medical Officer's safety review:

Endoscopic safety data are drawn from six endoscopy studies. The adequacy of study designs will be assessed as well as criteria used for endoscopic evaluation. Confounding co-morbid conditions, co-interventions and known prognostic factors will be addressed. Validation of endoscopic coding will be performed through a random sampling of 10% of all enrollees and all patients withdrawn for any reason from the endoscopic studies 021, 071 and 041. Study 021 was one of two twelve-week studies with baseline and end of study endoscopic examinations. Study 071 was one of two twelve-week studies with monthly interval endoscopic examinations. These two studies were part of the North American Trials. Study 041 was the international study with only end of study endoscopic examinations. These three trials represented different endoscopic protocols for validation. All primary endoscopy reports and coded study documents will be compared for accuracy of data transfer. All sponsor defined clinically significant UGI events, from all controlled trials, will be reviewed in view of the safety claims made based on these reports.

We are reviewing a new drug entity representing a possible major breakthrough in our understanding of the biology of inflammation and prostaglandin function. Safety data from the large number of patients in non-endoscopic studies are relevant since large numbers of observations are needed to establish statistically significant differences when it comes to the clinically relevant endpoints of bleeding, perforation, obstruction and death associated with the use of nonselective Cox inhibitors. Nonendoscopic safety data, other than the clinically significant UGI events, will be reviewed by the primary reviewing division.

III. General design and study definitions of endoscopic protocols

A. General study format

All endoscopy studies followed a similar format although the duration of studies varied. Some included placebo controls while some included only active comparators, depending on the efficacy and safety issues to be addressed. The international study (041) had some variances that will be noted. All studies involved randomization, and double blinding. Each study included doses that are claimed to be effective in the treatment of those conditions for which FDA approval is being requested. One endoscopic study (022)included a 2X dose

B. Study duration

The first endoscopic study reviewed was a pilot study in healthy volunteers of 1-week duration and is of no value in assessing long term safety. Four of the endoscopic studies were of 12 weeks duration and one international study was of 24 weeks duration. This 24-week study allowed for pre-protocol usage of NSAIDs and did not include a baseline endoscopy. This omission limits the value of this longest of endoscopic studies when assessing for asymptomatic endoscopically proven ulcers. This trial could give valuable data on the rate of adverse events, including serious adverse events over the longest period of time that this product has been studied in a controlled manner. It does reflect the setting that a drug will most likely be used in practice (absent endoscopic baseline).

Ideally, there should be longer- term data to assess GI safety. This is particularly important when reviewing a compound aimed at treating chronic, lifelong conditions and chronic pain. Some studies in the literature suggest that the incidence of GI adverse events stabilize within several months. There is no definitive evidence however of this claim. While mucosal changes occur within minutes of ingesting an NSAID, these acute changes, related to topical effects, are different than the development of clinically relevant ulcers, which take longer to occur. The protective and adaptive changes that may occur during longer duration of exposure to NSAIDs are not well understood. The possibility of upregulation and downregulation of the Cox isoforms and other enzymes in the prostaglandin cascade within the gastrointestinal mucosa makes it risky to extrapolate from safety data available from previously published literature on NSAIDs that might suggest that a 6 months study may be adequate to establish long term safety. There are studies that suggest a beneficial role for Cox-2 activity in the healing of gastric damage. Cox-2 inhibition may interfere with healing of gastric ulcers if this preliminary data is relevant to human physiology. The novelty of this area of medicine and pharmaceutical intervention makes it impossible to safely extrapolate very far from evidence based recommendations. Look term studies of the safety of Cox-2 would therefore be desirable.

C. Endoscopic parameters and important definitions:

Endoscopic parameters: The scoring system defined by the sponsor in table 1 refers only to the gastroduodenal mucosa and has been used in other studies in the medical literature. This system is used in all 5 pivotal endoscopic studies.

Table 1 (from study 021)

Table 2. Mucosal Scoring Scale

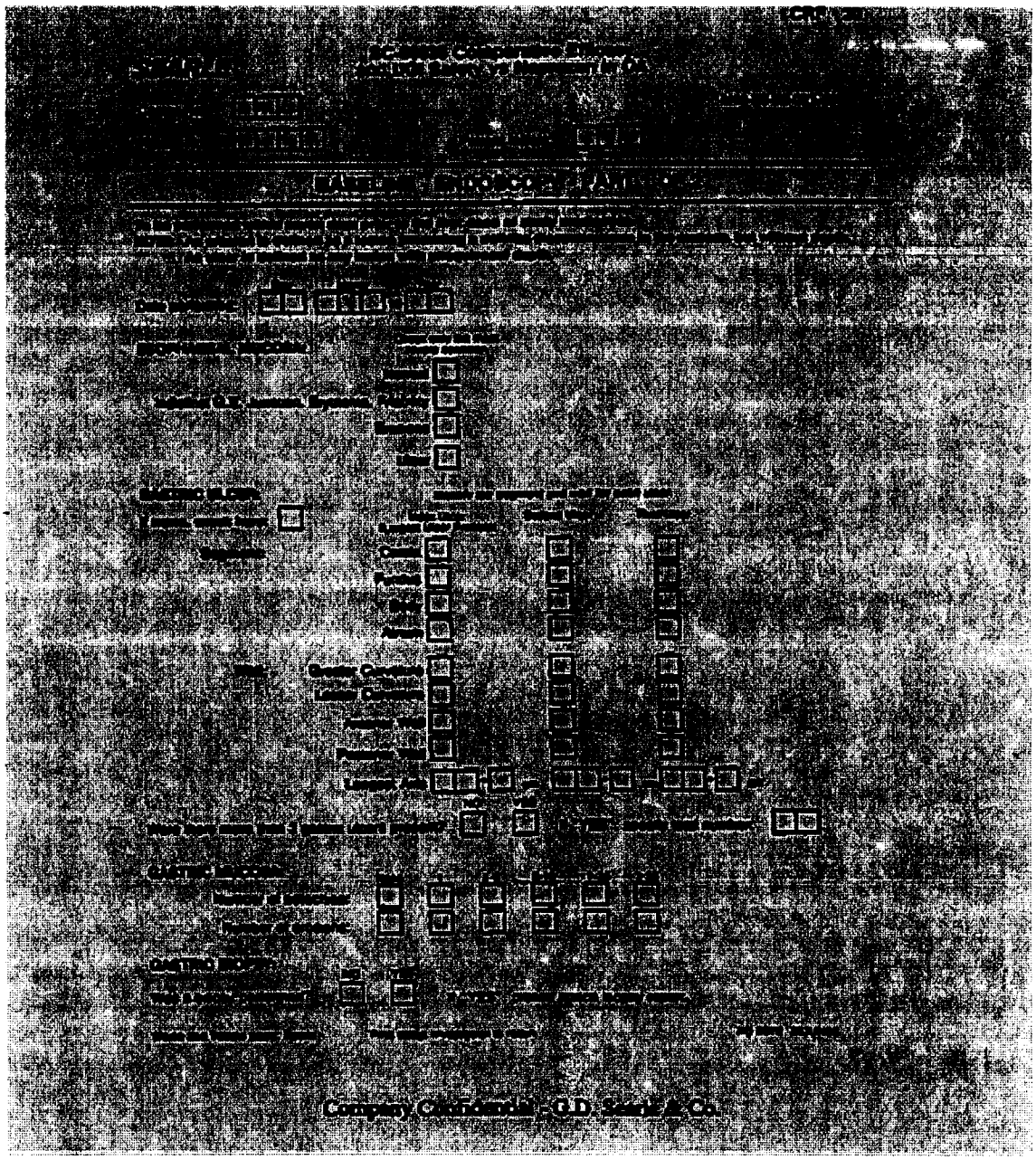
Grade	Description
0	No visible lesions (i.e., normal mucosa)
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions*
5	11-25 erosions*
6	>25 erosions*
7	Ulcer**

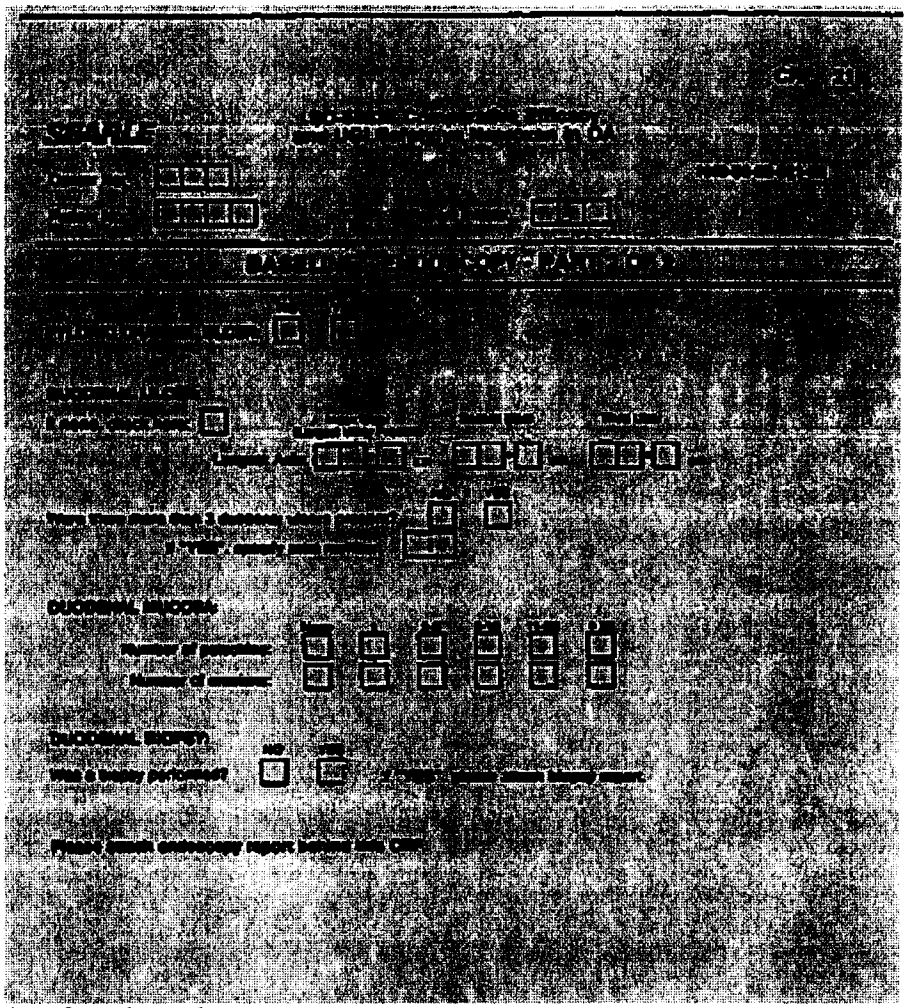
* An erosion was defined as any break in the mucosa without depth
** An ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth.

By definition endoscopic findings are subjective, relying on visual interpretation. There are no reliable methods to assess depth. The definition of erosion is even more subjective than the definition of an ulcer as defined by the sponsor. If depth is difficult to assess, than a break in the mucosa is even more difficult to assess. Requiring the presence of an exudate or white coating adjacent to normal pink mucosa would better define this entity. Counting erosions is difficult given the variability in size and observer ability to visualize them. The identification of petechiae is of less clinical relevance and even more subject to interobserver variability. The value of the 1 through 6 levels of the grading system above has not been validated for clinical meaning. Fortunately the bulk of analysis by the sponsor and the bulk of this reviewer's attention will be on the level 7 finding of an ulcer. At this time there are no better surrogates for the risk of clinically relevant upper gastrointestinal events than endoscopic findings. Therefore, even with the limitations as noted, these data, along with adverse event data are the best surrogate parameters to use in defining safety to the mucosa of the upper gastrointestinal tract. The optimal analysis would involve the relevant clinical endpoints themselves; significant bleeding, perforation, obstruction and death.

Esophageal endoscopy findings were also collected but were not based on this scoring system. The results were not included in the endoscopy analyses, as the sponsor did not define these as relevant endpoints. Although esophageal damage is within the constellation of NSAID induced pathology, the gastroduodenal effects have historically been considered the most serious and were chosen by the sponsor as the parameters of interest.

The endoscopy coding form reproduced below included both relevant and irrelevant data as defined in the protocols. None of the protocols define the number of ulcers or size as a parameter of interest and yet a large part of the forms are occupied by space for this information. As will be discussed later, many endoscopists did not collect the relevant data endpoint of the number of erosions and there were cases of mistaken coding and poorly legible primary source documents from which sponsors representatives had to transfer data. Direct data entry by the endoscopists would have eliminated some coding difficulties.





Important Definitions from the study text

Adverse Events

The Investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safety of the drug under investigation.

Types of Adverse Events

The term "adverse event" could include any of the following events that develop or increase in severity during the course of the study:

a. Any signs or symptoms, whether thought to be related or unrelated to the condition under study;
b Any clinically significant laboratory abnormality;
c. Any abnormality detected during physical examination.

Signs or Symptoms will be graded by the Investigator as mild, moderate, or severe according to the following definitions:

Grade: Definition

Mild: Causing no limitation of usual activities.
Moderate: Causing some limitation of usual activities.
Severe: Causing inability to carry out usual activities.

Serious Adverse Events

A "serious" adverse event is defined as any event that suggests a significant hazard, contraindication, side effect or precaution. A serious adverse event includes any event that:

a. Is fatal;
b. Is life threatening, meaning the patient was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death;
c. Is permanently disabling;
d. Requires, or prolongs, inpatient hospitalization;
e. Is a congenital anomaly;
f. Is a cancer;
g. Is an overdose.

Investigators were instructed to immediately report any event considered to represent a potentially clinically significant UGI event (defined as UGI bleeding, perforation, or gastric outlet obstruction). Data pertaining to the event were summarized and distributed in a blinded fashion to each of the Gastrointestinal Consultants to determine whether the event was a clinically significant UGI event. For all reviews, Committee members were blinded to which treatment patients had received.

The committee adjudicated all potentially clinically significant UGI events according to the following prospectively defined criteria:

1. UGI Bleeding
- hematemesis with a lesion* at endoscopy or x-ray,
- lesion at endoscopy with evidence of active bleeding or stigmata of a recent hemorrhage (visible vessel or clot attached to the base of an ulcer),
- melena with a lesion at endoscopy or x-ray,
- hemoccult positive stools with a lesion at endoscopy or x-ray with evidence of serious bleeding, which included:

i. fall in hematocrit over 5% (absolute change)
ii. signs of postural vital sign changes (increase of pulse rate of 30 bpm and a decrease in systolic blood pressure of 20 mm Hg and a diastolic blood pressure of 10 mm Hg)
iii. transfusion of more than two units of blood
iv. blood in the stomach

- A lesion is an ulcer or large erosion.

2. Perforation

This was a perforated lesion that required surgery. It could involve a laparoscopic repair, but only if evidence of the perforation were unequivocal such as free air in the abdomen visible by x-ray, or peritoneal signs upon physical examination.

3. Gastric Outlet Obstruction

Gastric outlet obstruction was required to be diagnosed by the Investigator, and the diagnosis had to be supported by endoscopy (e.g., a tight edematous ulcer in the pyloric channel) or by x-ray results (e.g., a dilated stomach, delayed barium emptying with clinical evidence of outlet obstruction and with ulcer in the channel or severe narrowing and edema).

(End of protocol text)

The definition of UGI bleeding was not well defined. The term hematemesis is defined as "the vomiting of blood and melena is defined as "the passage of dark, pitchy, and grumous stools stained with blood pigments or with altered blood" in the Dorland's Medical Dictionary. "Coffee ground emesis" is a generic term used to describe the appearance that blood may take when it has been in contact with the acid environment of the stomach. Blood turns brown and depending on other factors may take on the consistency of coffee grounds, stain other gastric contents brown or present as confluent brown material. The term melena was used in the relevant narrative summaries without reference to red blood or documentation that altered color of stool was even associated with the true presence of blood. The sponsor used the term "coffee ground emesis" at times without any reference to documentation of qualitative testing for heme contents. Ingested foodstuff such as coffee or chocolate may have the same appearance as acidified blood in the stomach and some foodstuffs will create a dark stool. In short, the appearance of brown or black emesis or stool alone is not adequate documentation of bleeding. The definition of UGI bleeding by the sponsor was incomplete in this regard. The sponsor's agents interpreting the clinical data assumed that coffee ground emesis was the same as hematemesis. When dealing with the most clinically relevant safety parameter of the entire submission clear definitions and strict attention to these definitions is critical. In the body of the review instances will be presented that represent this study flaw. Clinically relevant UGI bleeding is not the same as documentation of bleeding. Small volumes of blood can be intermittently lost from the UGI tract from transient lesions that are of no clinical consequence. The medical literature has documented this phenomenon in relation to single doses of aspirin or single episodes of alcohol intake. Numerous instances in the submission are documented where baseline endoscopies revealed scant amounts of blood on the surface of reddened or eroded mucosa. These were appropriately not excluded from the study but would meet the same criteria of UGI bleeding defined as a clinically significant UGI bleed in the definition section of the studies. A more appropriate definition would require a standardized quantitation of bleeding that would eliminate contamination of the meaningful endpoint with insignificant bleeding episodes.

Gastric outlet obstruction (GOO) was another Clinically significant UGI event defined poorly. The method of diagnosis by the investigator is not well stated. The diagnosis of GOO should include a consistent clinical presentation that is supported by diagnostic testing. A case report is presented later in the review where this lack of clinical definition resulted in an inappropriate classification.

D. Choice of comparators.

One endoscopic study used diclofenac 75mg. b.i.d. alone as active comparator. A second study used diclofenac 75mg. b.i.d., and ibuprofen 800mg. t.i.d.. Four studies used naproxen 500mg b.i.d. as the active

comparator. Two of these endoscopic studies were placebo controlled. The choice of comparators as well as the dose and dosing regimens of comparators were based on manufacturers recommended dosages. These are among the common NSAIDs in use According to the sponsor these three drugs represent over 50% of the prescription and over the counter medication usage for arthritis in this country. A limited list of comparators cannot test the universe of NSAIDs for safety compared to celecoxib but in combination with placebo controls the chosen active comparators may give very valuable information in testing the hypothesis of high Cox 2 selectivity for celecoxib. Unfortunately studies of comparative GI safety among the NSAIDs is not well controlled for similar dose/efficacy among the comparators. True relative safety data on the NSAIDs is flawed. This fact makes it difficult if not impossible to definitively compare a study drug to NSAIDs in a generic fashion.

IV. Review of individual trials

A. Study 014: A comparison of the effects of celecoxib 100 mg. BID, 200 mg BID, Naproxen 500mg BID and placebo on the upper gastrointestinal mucosa of healthy subjects.

This brief 1 week pilot safety study was designed to endoscopically assess the effects of celecoxib 100mg b.i.d. and 200mg. b.i.d. on the upper gastrointestinal tract in healthy individuals compared to placebo and an active comparator, naproxen 500mg. b.i.d. This dose of naproxen is a clinically effective and commonly used dosage regimen. A total of 128 subjects were randomized and bias was minimized by double blinding of the trial. Inclusion and exclusion criteria were appropriate for this type study. Criteria for evaluation included medical history, physical examination, diary cards, baseline and day 7 endoscopy as well as clinical laboratory tests including serologic testing for Helicobacter Pylori (H. pylori). Serologic testing gives data regarding past exposure to this pathogen but does not give adequately specific information about current infection to use in analyzing this potential confounding variable.

Results:

Endoscopy results: In this small pilot study the endoscopic safety profile of celecoxib at both doses was similar to that seen with placebo. The naproxen group had a gastric ulcer incidence of 19%. The placebo and celecoxib groups experienced no ulcers. Erosions also tended to be numerically higher in the naproxen group. In this small study there was no statistically significant correlation between H. pylori serology and ulcer incidence. As noted above, this information is of limited value.

Serious adverse events: There were no serious adverse events no withdrawals and no deaths.

This small brief Phase I study suggested a better GI safety profile for celecoxib compared to naproxen. It was too small to statistically assess comparability to placebo. These data will not be combined with any attempts to perform cross study analysis and will therefore have little impact on the overall assessment of celecoxib safety for long term use.

B. Study 021 A multicenter, double –blind placebo controlled , randomized comparison study of the efficacy and upper gastrointestinal safety of celecoxib 50mg, 100mg. and 200mg. b.i.d. and naproxen 500mg. b.i.d. in treating the signs and symptoms of osteoarthritis of the knee.

1.Study objectives as defined by sponsor (Protocol text)
Primary Objectives
a. Compare the efficacy of celecoxib 50 mg, 100 mg, and 200 mg BID with placebo in treating the signs and symptoms of OA of the knee;

b. Evaluate the UGI safety of celecoxib 50 mg, 100 mg, and 200 mg BID versus naproxen 500 mg BID and placebo in patients with OA of the knee; and in patients with OA of the knee.

Secondary Objectives

a. Compare the efficacy of naproxen 500 mg BID and placebo in treating the signs and symptoms of OA of the knee; and
b. Compare the efficacy of celecoxib 50 mg, 100 mg, and 200 mg BID with naproxen 500 mg BID in treating the signs and symptoms of OA of the knee.

(end of protocol text)

2.Study design: The outline of study procedures is presented in table 2.

Table 2 (from study 021)

Table 1. Schedule of Observations and Procedures

	Screening Visit Day -14 to -2	Baseline Visit Day 0	Week 2 Day 14 ±1 day	Week 6 Day 42 ±3 days	Week 12 Day 84 ±5 days	Early Termination
Informed Consent	X					
Medical History	X					
Physical Examination	X				X	X
Clinical Lab Tests (a)	X		X	X(b)	X	X
QOL Assessment (c)		X	X		X	X
OA Assessments	X(d)	X	X	X	X	X
UGI Endoscopy	X(e)				X	X
Discontinue NSAID or analgesic (f)	X					
Meet Flare Criteria		X				
Signs and Symptoms		X	X	X	X	X
APS Pain Measure (g)		X				
Patient Assessment of Function (g)		X				
Dispense Study Medication		X	X	X		
Return & Count Study Med			X	X	X	X
Dispense Concurrent Medications Diary Card		X	X	X		
Retrieve Concurrent Medications Diary Card			X	X	X	X

(a) Clinical laboratory tests included: Hematology (white blood cell [WBC] count with differential, red blood cell [RBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable], prothrombin time [PT], partial thromboplastin time [PTT]; Biochemistry (sodium, potassium, chloride, calcium, inorganic phosphorus, BUN, creatinine, total protein, albumin, total bilirubin, uric acid, glucose alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]; and Urinalysis (pH, specific gravity, WBC, RBC, protein, glucose, ketones, bilirubin). FlexSure at Baseline and CLOtest at Final Visit for H. pylori. Serum pregnancy test for women of childbearing potential at Screening Visit only.
(b) PT and PTT tests were not performed at the Week 6 Visit.
(c) SF-36 Health Survey and WOMAC Osteoarthritis Index.
(d) Screening Arthritis Assessment data were collected by Searle but not entered in the database. Patient's Assessment of Pain (VAS) was not performed at Screening Visit.
(e) Screening Visit UGI endoscopy must have been completed within 7 days of the first dose.
(f) Patients discontinued oxaprozin and/or piroxicam at least four days before the Baseline Arthritis Assessments.
(g) American Pain Society (APS) Pain Measure and Patient Assessment of Function were completed by the patient during the Baseline Visit and daily for the first seven days of dosing with study medication. (Patients enrolled prior to 29 August 1996 who already began taking study medication were not required to complete questionnaires.)

Inclusion and exclusion criteria are extracted from the protocols and presented in table 3.

Table 3.

Inclusion and exclusion criteria as derived from protocol 021

Inclusion Criteria	Exclusion Criteria
1. Been of legal age and consent: 2. If female and of childbearing potential, been using adequate contraception 3. Been diagnosed according to the ACR criteria as having OA of the knee. 4. Had a functional capacity classification of I-III at the baseline visit: 5. Had OA in a flare state at the baseline visit. 6. Provided written informed consent before undergoing any study procedure:	1.Had been diagnosed with any inflammatory arthritis or gout or any acute joint trauma at the knee or hip with OA 2. An anticipated need for any surgical or other invasive procedure (e.g. arthroscopy or lavage that would have been performed on the hip and/or knee with OA during the course of the study 3.Received oral, intramuscular, intra- articular, or soft tissue injections of corticosteroids within the four weeks before the first dose of study medication 4.Taken any NSAIDs or any analgesic within 48 hours before the Baseline Arthritis Assessments.(patients taking325 mg aspirin per day for non-arthritic reasons, if stable for at least 30 days before the first dose of study medication, were allowed to continue their aspirin regimen for the duration of the study. Patients must have discontinued piroxicam and/or oxaprozin at least four days before the Baseline Arthritis Assessments 5.Had an active malignancy of any type or history of malignancy. (Patients who had a history of basal cell carcinoma that had been treated were eligible. Patients with a history of other malignancies that had been surgically removed and who had no evidence of recurrence for at least five years before study enrollment were also eligible.) 6.Had been diagnosed with or had been treated for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days before receiving the first dose of study medication 7. Had active GI disease(e.g. inflammatory bowel disease) or had an esophageal, gastric, pyloric channel or duodenal ulcer(defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth) or more than 10 erosions in the stomach, or more than ten erosions in the duodenum on the baseline endoscopy 8. Had a history of gastric or duodenal surgery other than simple oversew 9. Had acute or chronic renal failure Hepatic disease, or a coagulation disorder Abnormal screening lab values >1.5 x upper limits of normal(ULN) for either AST or ALT or any other lab abnormalities considered to be clinically significant by the investigator within 14 days before the Baseline Arthritis Assessment 10. Had a known hypersensitivity to COX-2 inhibitors, sulfonamides or NSAIDs 11. Had received or was scheduled to receive any other investigational drug during the course of the study 12. Had previously been admitted to this study

Once these criteria were met, enrolled patients underwent baseline endoscopy and again at the end of the study or at the time of early termination. All ulcers found at any point during the study were carried forward to be included in the final ulcer rates. If an ulcer was identified prior to the end of the study; the patient was withdrawn. Ulcers found at the time of early termination endoscopy were not, however, included in the adverse event reporting unless they were found at an endoscopy for evaluation of GI symptoms.

Endoscopic data were analyzed in relation to treatment as well as multiple assumed ulcer risk factors including H. pylori status (serology at entry and CLOtest at final endoscopy), age, history of cardiac disease, gastroduodenal ulcer disease, NSAID GI intolerance, gastrointestinal bleeding and aspirin use during the study. Unfortunately neither baseline population status or ulcer incidence data was available in relation to alcohol or tobacco use. This reviewer considers this to be a significant flaw in the study design of all the submitted endoscopic studies as there exist significant data in the medical literature on ulcer disease regarding the relative risks associated with alcohol and tobacco use.

Information obtained on low dose aspirin use was based on patient volunteered information written on a concurrent medication diary card as described below. Many patients would not consider prophylactic aspirin therapy when filling out such a diary and aspirin use may be significantly underreported.

The original protocol was amended after the study was begun to change criteria for endoscopic evaluability. Initially screened patients with more than 10 erosions were excluded from the study and hence endoscopic evaluability. The final protocol included such patients. Also, initially protocol deviations that included the use of any anti-ulcer drugs or antacids would have been grounds for exclusion from endoscopic evaluability. Administrative change #4 modified these exclusions. Following the change only participants taking anti-ulcer or antacids for more than three consecutive days since prior visit or for a total of five days during the entire study were excluded from endoscopic evaluability .The protocol changes expand the definition of endoscopic evaluability in a retrospective manner. The effect of retrospectively altering a major protocol to include patients with more than 10 erosions is unclear. One would expect randomization to affect all groups similarly. The inclusion of patients who took "low dose " anti-ulcer medication or antacids would presumably increase the cohort size and have unknown effects on the statistical results.

The use of drugs other than study medication was discouraged during the screening and treatment periods. The following drugs were specifically prohibited:

1. NSAIDs (other than 325 mg aspirin per day for nonarthritic reasons);
2. Oral or injectable corticosteroids;
3. Analgesics (Acetaminophen up to 2 g/day may have been taken for reasons other than arthritis, only if absolutely necessary, and for no more than three consecutive days. Acetaminophen must have been avoided within 48 hours prior to arthritis assessments performed at any visit.) Patients were not to use an analgesic for relief of arthritis symptoms;
4. Anticoagulants; and
5. Anti-ulcer drugs.

The use of any medications other than study medication was to be recorded on a Concurrent Medications Diary Card which included the drug name, dosage, regimen, reason for therapy and therapy dates.

3. Results:

i. Patient demographics: Patient groups were comparable in

regards to age, sex, history of NSAID intolerance, history of gastroduodenal ulcer, history of GI bleed, cardiovascular disease, baseline endoscopy scores, race, and H. pylori status (serologic test). Patient demographics were not given on tobacco use, aspirin use and alcohol use.

ii. Patient disposition: 1215 patients were enrolled in this study but protocol changes limiting the study to only patients with OA (and excluding hip patients) symptomatically involving the knee dropped the efficacy cohort down to 1192 but the endoscopy cohort remained at 1215. Each of the four groups contained between 226 to 252 patients. 384 or 32% patients withdrew from the study (24% due to lack of efficacy and 8% due to adverse events).

The number of patients endoscopically evaluable was ultimately even smaller. Twelve week ulcer data are available for 104 or 42% of placebo, 159 or 62%- 50mg b.i.d. celecoxib, 152 or 64% of-100 mg b.i.d celecoxib, 146 or 62% of - 200mg b.i.d celecoxib and 134 or 58% of naproxen 500mg b.i.d participants.

All ulcers identified at any point during the study are carried over to the end of study to give crude ulcer rates.

iii. **Serious UGI Adverse events**

All such described events were reviewed case by case. Only one case was felt by this reviewer to be related to any of the study drugs. The clinical summary is found below as it appeared in the submission:

(from text of study021)
Patient No. US0004-0662 DER 970723-CL499 (Abdominal Pain, Gastritis, Gastric Ulcer, Ileus) was a 49 year old female with a history of OA, ulcer, and nerve problems. The patient was enrolled into the study on 24 April 1997 and randomized to receive SC-58635 200 mg BID. After 79 days of treatment the patient was hospitalized with stomach pain and distention and was discharged two days later. The Week 12 endoscopy was performed the following day and revealed hiatal hernia and diffuse gastritis with small 0.2 cm gastric ulcer without active bleeding (endoscopy report says 'not sure about the ulcer' but later confirmed presence of ulcer). The patient started famotidine the same day. A follow-up visit on 21 Sept 1997 included the following diagnostic tests: an unremarkable chest x-ray; an x-ray of the abdomen that suggested a localized ileus in the mid-abdomen; CBC with differential, PT/PTT, creatinine kinase, cardiac troponin 1, urinalysis, amylase, and lipase were normal. Chemistry profile was normal except for low potassium of 3.5, elevated calculated globulin of 4.1, and elevated lactic dehydrogenase of 242. Concomitant medications included albuterol, nifedipine, gabapentin, sertraline hydrochloride and trazodone hydrochloride. The patient completed the study and according to the study coordinator is "feeling much better." The patient has recovered. The Investigator determined there was a probable association between the event and the study medication and the Searle Medical Monitor was uncertain regarding the possibility of a relationship with study medication.
(end of text of study 021)

The endoscopy reports on this patient were reviewed. The baseline endoscopy revealed 6 erosions in the pyloric area. The remainder of the examination was totally normal. The week 12 endoscopy that occurred during the hospitalization for this adverse event revealed the gastric ulcer noted above. This was a new finding in addition to the gastric erosions seen at baseline. In addition the duodenal endoscopy revealed three new erosions not present during the baseline exam. The small size of the ulcer (under 3mm) technically excluded this patient from qualifying

as having developed an ulcer in this study protocol. This reviewer found it striking that this event was not felt to be definitely or likely related to the study drug by the Searle monitor.

This reviewer concludes that there was one "serious" UGI event related to a study medication: celecoxib. No clinically significant UGI events, as defined by the protocol occurred during this study. One patient death occurred during the study. This death occurred due to complications following surgery for a gangrenous gall bladder and is felt unrelated to the study or study medication

iv. Endoscopy

Data validation

An audit of the endoscopy source documents and coding sheets was conducted to validate the endoscopic data. Reports from 516 patients out of the 1193 patients enrolled in the study were reviewed. This included 10% of all patients enrolled and all withdrawn patients. A total of 942 reports were reviewed. 5% of reports were missing either the source document or the case report form for auditing. In 3% of the reports reviewed there were coding discrepancies. The majority of these discrepancies involved extrapolation by the coding person of imprecise reports. The coding sheet and study protocol required quantitating the number of erosions present. One of the endpoints of the study was the overall endoscopy score as defined earlier in this review. The source documents for endoscopy were not standardized and each endoscopist dictated or hand wrote their reports. In 18 cases the endoscopist did not quantify the number of erosions. Terms such as "a few", "several" or "multiple" were used. This coding process made it necessary for the coders to extrapolate to an absolute number in order to complete the case report forms. This makes the data on endoscopic score difficult to interpret accurately. Two cases of miscoding were identified where ulcers were noted on source documents but transferred to the case report forms as erosions. One of these was in the placebo group and one was in the naproxen group. This represents a 3% (2/69 total ulcers identified) error rate assuming that this audit is representative. The blinded nature of this study mitigates these flaws to some extent. There is no apparent pattern of miscoding and no study is without human error. There are no standards of acceptable error rates in clinical trials. Endoscopic measuring devices and video endoscopy may have been helpful in resolving coding questions that arose after the endoscopies were completed. A complete audit of all endoscopic data could be requested although the data are now unblinded. Correction for the uncovered errors is also possible although the incomplete nature of the audit leaves other possible errors uncorrected and adds a potential bias since the audit included all withdrawals and only 10% of completed patients. The errors as identified do not change the significance of the study results. The least confounding management of this issue is to note the results of this audit for future consideration and assessment of these studies. Future studies would benefit from the use of photographic aids for all endoscopies as well as measuring devices when size of a lesion is relevant. Careful attention by the endoscopists to the details required by the protocols would also improve the accuracy of data collection.

Endoscopy results

Table 4 (from study 021)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 1 OF 7: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL

INTENT-TO-TREAT COHORT (ITT) – KNEE AND HIP PATIENTS

	PLACEBO (N=247)		SC-58635 50MG BID (N=258)		SC-58635 100MG BID (N=239)		SC-58635 200MG BID (N=237)		NAPROXEN 500MG BID (N=233)	
	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ul cer
Study Days										
WK2 (2-28)	63	1	30	2	30	1	25	2	19	2
WK6 (29-76)	37	1	32	3	34	3	40	2	34	10
WK12 (77-91)	102	2	156	3	148	3	137	9	112	22
(>91)	10	2	7	0	8	9	5	9	11	9
TOTAL	212	5	225	8	220	7	208	13	176	34

Table 5 (from study 021)

SC-58635 COMPARATIVE EFFICACY AND GI SAFETY VS NAPROXEN IN OA
M49-96-02-021

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS (a)
PART 2 OF 7: ANALYSIS OF CRUDE ULCER RATE

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)	SC-58635 50MG BID (N= 258)	SC-58635 100MG BID (N= 239)	SC-58635 200MG BID (N= 237)	NAPROXEN 500MG BID (N= 233)	OVERALL p-VALUE (c)
WEEK 12						
CRUDE ULCER RATE(a):						<0.001
NO ULCER	102(96%)	156(95%)	148(95%)	137(91%)	112(77%)	
ULCER	4(4%)	8(5%)	7(5%)	13(9%)	34(23%)	
UNKNOWN (WITHOUT ENDO/WITH ENDO)	141(41/100)	94(32/ 62)	84(20/ 64)	87(22/ 65)	87(34/ 53)	
FINAL						
CRUDE ULCER RATE(b):						<0.001
NO ULCER	212(98%)	225(97%)	220(97%)	208(94%)	176(84%)	
ULCER	5(2%)	8(3%)	7(3%)	13(6%)	34(16%)	
UNKNOWN (WITHOUT ENDO/WITH ENDO)	30(30/ 0)	25(25/ 0)	12(12/ 0)	16(16/ 0)	23(23/ 0)	

p-VALUES FOR TREATMENT COMPARISONS (d):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 12 :	0.781	0.173	0.644	0.992	0.204	0.233	<0.001	<0.001	<0.001	<0.001
FINAL :	0.642	0.073	0.472	0.903	0.168	0.221	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer;Ulcer: ulcer detected prior to or within the visit window; Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient
(c) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis
(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Table 6 (from study 021)

TABLE 34
GASTRIC ENDOSCOPY RESULTS (a) (b)
PART 1 OF 10: MEANS AND FREQUENCY DISTRIBUTION

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)	SC-58635 50MG BID (N= 258)	SC-58635 100MG BID (N= 239)	SC-58635 200MG BID (N= 237)	NAPROXEN 500MG BID (N= 233)	p-VALUE (c)
WEEK 12						
N, MEAN (STD DEV)	106,1.2 (1.82)	164,1.1 (1.92)	155,1.3 (1.87)	148,1.4 (2.08)	141,3.1 (2.52)	
FREQUENCY DISTRIBUTION						<0.001
0 (NO VISIBLE LESIONS)	68(64%)	107(65%)	89(57%)	84(57%)	41(29%)	
1 (1-10 PETECHIAE)	6(6%)	17(10%)	19(12%)	16(11%)	6(4%)	
2 (>10 PETECHIAE)	2(2%)	3(2%)	3(2%)	6(4%)	4(3%)	
3 (1-5 EROSIONS)	22(21%)	21(13%)	30(19%)	22(15%)	31(22%)	
4 (6-10 EROSIONS)	2(2%)	2(1%)	5(3%)	7(5%)	16(11%)	
5 (11-25 EROSIONS)	2(2%)	5(3%)	1(<1%)	2(1%)	17(12%)	
6 (>25 EROSIONS)	0(0%)	1(<1%)	1(<1%)	1(<1%)	1(<1%)	
7 (ULCER)	4(4%)	8(5%)	7(5%)	10(7%)	25(18%)	
UNKNOWN	141	94	84	89	92	

p-VALUES FOR TREATMENT COMPARISONS (d):

100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
0.338	0.438	0.999	0.208	0.298	0.862	<0.001	<0.001	<0.001	<0.001

(a) The last observation carried forward approach is used for known ulcer only
(b) Score ranged from 0 (no visible lesions) to 7 (ulcer)
(c) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ) 'UNKNOWN' patients were excluded
(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ) 'UNKNOWN' patients were excluded

These data display a significant difference in ulcer rate and overall endoscopy score between naproxen and all three doses of celecoxib. Survival analysis revealed a higher 12 week and cumulative ulcer rate than did the simple analysis noted in table 5. Based on a survival analysis the gastroduodenal ulcer rates are 5.6% for placebo, 8.1% for celecoxib 50mg 5.1% for celecoxib 100mg and 12.4% for celecoxib 200mg and 33.8% for naproxen. Refer to table 7. The study design did not power the data to pick up statistically significant differences in ulcer rates among the different doses of celecoxib and compared to placebo. Even with this underpowering effect, the difference between placebo and the celecoxib 200-mg group almost reached statistical significance. The absolute difference in final crude ulcer rates between placebo and celecoxib groups 50-mg, 100 –mg and 200mg doses was 50%, 50% and 300% respectively. Combining celecoxib groups the final ulcer rate was 4% (or 200 % higher than the ulcer rate in placebo). The trend of higher ulcer rates in the highest dose celecoxib group seen in this study is not a pattern seen in other studies.

Table 7 (from study021)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 4 OF 7: CUMULATIVE ULCER RATE BASED ON KAPLAN-MEIER ESTIMATES AND TREATMENT COMPARISON

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)	SC-58635 50MG BID (N= 258)	SC-58635 100MG BID (N= 239)	SC-58635 200MG BID (N= 237)	NAPROXEN 500MG BID (N= 233)	p-VALUE (a)
RATE BASED ON KAPLAN-MEIER ESTIMATES (b)						
WEEK 12	5.6%	8.1%	5.1%	12.4%	33.8%	<0.001

p-VALUES FOR TREATMENT COMPARISONS AT WEEK 12 (a)

100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
0.616	0.069	0.466	0.861	0.186	0.157	<0.001	<0.001	<0.001	0.002

(a) From Log-rank test
(b) Rates were read at the time point right after day 91 from the Kaplan-Meier curve. Time to event is censored at day 91 if corresponding endoscopy was performed after day 91

Table 8 (from study 021)

GASTRIC ENDOSCOPY RESULTS
PART 6 OF 10: FREQUENCY DISTRIBUTION BY H. PYLORI STATUS AS DETERMINED BY BOTH THE FLEXSURE AND CLO TESTS (a) (b)

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)		SC-58635 50MG BID (N= 258)		SC-58635 100MG BID (N= 239)		SC-58635 200MG BID (N= 237)		NAPROXEN 500MG BID (N= 233)	
FREQUENCY DISTRIBUTION	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
WEEK 12										
0	11(61%)	47(66%)	22(55%)	62(67%)	16(64%)	55(56%)	15(47%)	55(63%)	13(36%)	18(23%)
1	2(11%)	2(3%)	7(18%)	7(8%)	1(4%)	13(13%)	3(9%)	8(9%)	1(3%)	5(6%)
2	0(0%)	1(1%)	1(3%)	2(2%)	0(0%)	3(3%)	2(6%)	2(2%)	2(6%)	2(3%)
3	2(11%)	17(24%)	5(13%)	13(14%)	6(24%)	16(16%)	6(19%)	12(14%)	5(14%)	22(28%)
4	1(6%)	1(1%)	1(3%)	1(1%)	2(8%)	2(2%)	2(6%)	5(6%)	1(3%)	11(14%)
5	0(0%)	1(1%)	3(8%)	2(2%)	0(0%)	1(1%)	0(0%)	1(1%)	4(11%)	11(14%)
6	0(0%)	0(0%)	0(0%)	1(1%)	0(0%)	1(1%)	1(3%)	0(0%)	0(0%)	0(0%)
7	2(11%)	2(3%)	1(3%)	5(5%)	0(0%)	7(7%)	3(9%)	4(5%)	10(28%)	11(14%)
TOTAL	18(100%)	71(100%)	40(100%)	93(100%)	25(100%)	98(100%)	32(100%)	87(100%)	36(100%)	80(100%)

p-VALUE FOR H. PYLORI EFFECT ON ENDOSCOPY SCORE FROM ANOVA (c): 0.230
p-VALUE FOR H. PYLORI BY TREATMENT INTERACTION FROM ANOVA (d): 0.267
p-VALUE FOR H. PYLORI EFFECT ON ENDOSCOPY SCORE FROM CMH (e): 0.190

(a) The last observation carried forward approach is used for known ulcer only
(b) Positive (negative) patients should test positive (negative) by both the Flexsure and CLO tests. In all other cases, including missing test result or missing endoscopy, patients are categorized as unknown which result in removal from the H. Pylori effect analysis
(c) From Analysis of Covariance model with treatment, center and H. Pylori as factors and Baseline value as covariate, patients with unknown endoscopy are excluded
(d) From Analysis of Covariance model with factors treatment, center and H. Pylori and H. Pylori by treatment interaction as factors and Baseline value as covariate, 'UNKNOWN' patients are excluded
(e) From Cochran-Mantel-Haenszel test stratified by Baseline status and treatment (p-value from Row Mean Scores Differ),

Table 9 (from study 021)

TABLE 34
GASTRIC ENDOSCOPY RESULTS
PART 7 OF 10: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE AS DETERMINED BY BOTH THE FLEXSURE AND CLO TESTS (a) WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N= 247)	SC-58635 50MG BID (N= 258)	SC-58635 100MG BID (N= 239)	SC-58635 200MG BID (N= 237)	NAPROXEN 500MG BID (N= 233)	p-VALUE (d)
WEEK 12 CRUDE ULCER RATE BY H. PYLORI STATUS:						0.334
POSITIVE	11.1% (2/ 18)	2.5% (1/ 40)	0.0% (0/ 25)	9.4% (3/ 32)	27.8% (10/ 36)	
NEGATIVE	2.8% (2/ 71)	5.4% (5/ 93)	7.1% (7/ 98)	4.6% (4/ 87)	13.8% (11/ 80)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.213	0.349	0.160	0.360	0.093	
WEEK 12 OBSERVED MEAN GASTRIC SCORE BY H. PYLORI STATUS:						
POSITIVE	1.4	1.3	1.1	1.9	3.2	
NEGATIVE	1.1	1.1	1.4	1.2	3.1	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (c)	0.582	0.921	0.749	0.013	0.865	

(a) Positive (negative) patients should test positive (negative) by both the Flexsure and CLO tests. In all other cases, the patients are excluded from the H. Pylori effect analysis
(b) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ), patients with unknown endoscopy are excluded
(c) From Analysis of Covariance model with treatment, center, H. Pylori and H. Pylori by treatment interaction as factors, and Baseline value as covariate, patients with unknown endoscopy are excluded
(d) Overall H. Pylori effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by Baseline score and treatment (p-value from Row Mean Scores Differ), patients with unknown endoscopy are excluded

Interestingly, H. Pylori status did not have any statistically significant influence on the ulcer incidence in any group. While one could analyze tables 8 and 9 above to look for trends, the results from the other endoscopic studies do not support the suggestion of a statistically significant relationship between ulcer rates in this submission and H. pylori status based on serology or the concordance of serology and CLO testing or CLO testing and histology. It is unclear if this is due a true lack of correlation between H.pylori

infection and NSAID or non-NSAID related ulcers in this population. The large effect of naproxen and the small size of the endoscopy cohorts may obscure a true effect. There could be methodology issues as well. The issue of H. pylori infection and ulcer rates in this study will be discussed later in this review.

The data on aspirin use is summarized in Table 10. There appears to be a relationship between aspirin use and ulcer incidence in the placebo group and in the celecoxib 50mg and 200mg groups. No relationship was seen in the celecoxib 100mg dose and the naproxen groups. The nonagressive approach employed in this study to elicit a history of aspirin use may have resulted in inaccurate information. Review of the other 12-week endoscopic studies also reveals inconsistent results. Study 22 revealed no relationship between aspirin use and ulcers in the celecoxib groups while all 37 ulcers in the naproxen group occurred in the non-aspirin group (37/194) and 0/16 patients on naproxen and aspirin had ulcers. Study 062 revealed the anticipated relationship between aspirin use and ulcers in all groups (either as a trend or statistically significant relationship). Study 071 revealed no apparent meaningful correlations. Study 041 did not provide such data for analysis since no aspirin was allowed in that protocol. This reviewer suspects lack of statistical power accounts for the results above findings: however with the new molecular entity celecoxib and its asserted cyclooxygenase selectivity; a true biologic phenomena may be missed when considering the effects of concomitant aspirin (or NSAID) and celecoxib usage. This issue will be addressed later in the review.

Table 10 (from study 021)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7.1 OF 7: COMPARISON OF PATIENTS WHO USED ASPIRIN VS. NOT WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT) - KNEE AND HIP PATIENTS

	PLACEBO (N=247)	SC-58635 50MG BID (N=258)	SC-58635 100MG BID (N=239)	SC-58635 200MG BID (N=237)	NAPROXEN 500MG BID (N=233)	p-VALUE (b)
WEEK 12 CRUDE ULCER RATE BY STATUS:						0.136
USE ASPIRIN	14.3% (2/ 14)	15.8% (3/ 19)	4.8% (1/ 21)	20.8% (5/ 24)	16.7% (5/ 30)	
NOT USE ASPIRIN	2.2% (2/ 92)	3.4% (5/145)	4.5% (6/134)	6.3% (8/126)	25.0% (29/116)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.012	0.041	0.927	0.056	0.358	
FINAL CRUDE ULCER RATE BY STATUS:						0.059
USE ASPIRIN	6.1% (2/ 33)	10.7% (3/ 28)	3.2% (1/ 31)	15.2% (5/ 33)	13.9% (5/ 36)	
NOT USE ASPIRIN	1.6% (3/184)	2.4% (5/205)	3.1% (6/196)	4.3% (8/188)	16.7% (29/174)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.096	0.050	0.941	0.036	0.763	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ)
(b) Overall effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ)

Data were provided on the correlation between ulcer incidence in all groups and previously identified risk factors. These risk factors included age, cardiovascular disease, prior GI bleeding, prior ulcer disease, and prior GI intolerance to NSAIDs. Interestingly, the current study did not reveal the same relationships except in two instances. Cardiovascular disease did statistically correlate with gastric ulcer in the naproxen group while trending in the celecoxib 200mg. group. A history of ulcer disease statistically correlated with duodenal ulcer incidence in the celecoxib 200mg group and trended in the naproxen group.

vi. **Summary:** In study 021 celecoxib usage was shown to be associated with a statistically significantly lower ulcer rate at all doses employed than naproxen 500mg. Celecoxib usage was associated with a higher ulcer rate than placebo. The magnitude did not reveal statistical significance. None of the studies in this submission were powered to reveal statistically significant differences between celecoxib and placebo. One serious UGI adverse event occurred in the study. This was in the celecoxib 200mg bid group.

C. Study 022: A multicenter, double blind, placebo controlled, randomized comparison study of the efficacy and upper gastrointestinal safety of celecoxib 100mg, 200mg and 400mg b.i.d. and naproxen 500mg b.i.d. in treating the signs and symptoms of Rheumatoid Arthritis :

1. Study objectives: (From study 022 text)

Primary Objectives

The primary objectives of this study were to:

1. Compare the efficacy of celecoxib 100 mg, 200 mg, and 400 mg BID with placebo in treating the signs and symptoms of RA;
2. Evaluate the UGI safety of celecoxib 100 mg, 200 mg, and 400 mg BID versus naproxen 500 mg BID and placebo in patients with RA; and
3. Evaluate the safety of celecoxib 100 mg, 200 mg, and 400 mg BID for 12 weeks in patients with RA.

Secondary Objectives

The secondary objectives of this study were to:

1. Compare the efficacy of naproxen 500 mg BID and placebo in treating signs and symptoms of RA; and
2. Compare the efficacy of celecoxib 100 mg, 200 mg, and 400 mg BID with naproxen 500 mg BID in treating the signs and symptoms of RA.

(end of study text)

2. Study design:

The study design was similar to study 021with modifications appropriate for the differences between rheumatoid arthritis and osteoarthritis. Most importantly, patients were enrolled while on multiple medications including corticosteroids, methotrexate, penicillamine, azothioprine, gold, antimalarials and sulfasalazine as long as the doses were stable over greater than a month and changes were not made during the study period. The same administrative changes related to defining endoscopic evaluability were made as noted in the review of study 021. The current study was concluded less than two months after the changes. Endoscopic criteria used in this study are outlined in study 021.

The higher dosage regimen included in this study (400mg b.i.d.) for celecoxib may allow for a better assessment of possible dose related trends seen in 021; assuming that the different study population does not impact on pathophysiology of NSAID related ulcers. The chronic inflammatory process involved in Rheumatoid Arthritis and concomitant medications may or may not increase susceptibility of patients to NSAID related ulcers. Comparisons between celecoxib and placebo will be particularly interesting and informative in relation to the type of arthritis.

3. Results

i. Demographics:

Patient groups were comparable in regards to age, sex, history of NSAID intolerance, history of gastroduodenal ulcer, history of GI bleed, cardiovascular disease, baseline endoscopy scores, race, and H. pylori status (serologic test) and concurrent use of DMARDs as outlined in the protocol. Similar to study 021, patient demographics was not given on tobacco use, aspirin use and alcohol use.

ii. Patient disposition: 1149 patients were enrolled. 61% completed the study with 345 withdrawing due to lack of efficacy and 65 withdrawing due to adverse events. Only 43% of the 231placebo enrollees, 61% of the 240 celecoxib 100-mg b.i.d.enrollees, 61% of the 235 celecoxib 200-m b.i.d.enrollees, 58% of the 218 celecoxib 400mg b.i.d and 60% of the 225 naproxen treated patients had endoscopy data from the final 12th week of the study.

iii. Serious UGI events:

There were no deaths, or serious UGI adverse events related to the study medication or clinically significant UGI events in this study.

iv. Endoscopy Results:

Table 11, 12, 13 provides clear evidence of a difference between the study groups in endoscopic parameters. There is a statistically significant higher gastroduodenal ulcer rate in the naproxen group compared to all other groups. The lack of significantly higher endoscopic scores or ulcer rate with the 400mg dose of celecoxib is of special note. The placebo and celecoxib study groups were not statistically different from one another. As in study 021, there was a slightly higher gastroduodenal ulcer rate in the celecoxib groups compared to placebo. Compared to placebo, the celecoxib 100mg, 200mg and 300 mg groups had a 100%,50% and 100% higher final ulcer incidence. Combining all celecoxib groups and comparing them to placebo the risk was 80% high in the celecoxib treated patients (4/200 or 2% vs. 23/639 or 3.6%). Unlike study 021, the survival analysis reveals a divergence from the crude rate for the celecoxib and naproxen groups but not placebo group. The rates based on survival analysis are more than double the crude rates of cumulative ulcers at 12 weeks. To some extent this reflects the study design whereby only symptomatic ulcer would be picked up early and all asymptomatic ulcers were only identified at the end of the study. This would suggest that celecoxib associated ulcers are less symptomatic (similar to what is known about NSAID related ulcers) than ulcers in patients not on any therapy. It is unknown whether an addition physiologic effect is causing the higher ulcer rates in the survival analysis. The fact that both celecoxib and naproxen reveal higher survival rates than the placebo group would suggest a lack of true equivalence between celecoxib and placebo when it comes to UGI toxicity. Since study 021 did not reveal this survival analysis effect, these conclusions are speculative. The studies are consistent however, in their differing ulcer rates for celecoxib and placebo.

Table 11 (study 022)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS (a)
PART 2 OF 7: ANALYSIS OF CRUDE ULCER RATE

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N= 231)	SC-58635 100MG BID (N= 240)	SC-58635 200MG BID (N= 235)	SC-58635 400MG BID (N= 217)	NAPROXEN 500MG BID (N= 225)	OVERALL p-VALUE (c)
WEEK 12						
CRUDE ULCER RATE(a):						<0.001
NO ULCER	95(95%)	139(94%)	139(96%)	122(94%)	101(74%)	
ULCER	4(4%)	9(6%)	6(4%)	8(6%)	36(26%)	
UNKNOWN (WITHOUT ENDO/WITH ENDO)	132(36/ 96)	92(22/ 70)	90(28/ 62)	87(24/ 63)	88(22/ 66)	
FINAL						
CRUDE ULCER RATE(b):						<0.001
NO ULCER	196(98%)	214(96%)	213(97%)	189(96%)	173(82%)	
ULCER	4(2%)	9(4%)	6(3%)	8(4%)	37(18%)	
UNKNOWN (WITHOUT ENDO/WITH ENDO)	31(31/ 0)	17(17/ 0)	16(16/ 0)	20(20/ 0)	15(15/ 0)	

p-VALUES FOR TREATMENT COMPARISONS (d):

	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
WEEK 12	0.829	0.434	0.482	0.554	0.883	0.666	<0.001	<0.001	<0.001	<0.001
FINAL	0.539	0.230	0.200	0.526	0.966	0.582	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer;Ulcer: ulcer detected prior to or within the visit window; Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient
(c) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis
(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Table 12 (study 022)

TABLE 34
GASTRIC ENDOSCOPY RESULTS (a) (b)
PART 1 OF 10: MEANS AND FREQUENCY DISTRIBUTION

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N= 231)	SC-58635 100MG BID (N= 240)	SC-58635 200MG BID (N= 235)	SC-58635 400MG BID (N= 217)	NAPROXEN 500MG BID (N= 225)	p-VALUE (c)
WEEK 12						
N, MEAN (STD DEV)	99,1.0 (1.71)	147,1.0 (1.75)	144,0.9 (1.65)	130,1.1 (1.89)	134,3.3 (2.53)	
FREQUENCY DISTRIBUTION						<0.001
0 (NO VISIBLE LESIONS)	60(61%)	95(65%)	96(67%)	81(62%)	30(22%)	
1 (1-10 PETECHIAE)	14(14%)	19(13%)	16(11%)	18(14%)	12(9%)	
2 (>10 PETECHIAE)	6(6%)	2(1%)	4(3%)	2(2%)	6(4%)	
3 (1-5 EROSIONS)	12(12%)	21(14%)	18(13%)	17(13%)	31(23%)	
4 (6-10 EROSIONS)	0(0%)	2(1%)	3(2%)	4(3%)	14(10%)	
5 (11-25 EROSIONS)	4(4%)	2(1%)	3(2%)	0(0%)	10(7%)	
6 (>25 EROSIONS)	0(0%)	0(0%)	0(0%)	1(<1%)	2(1%)	
7 (ULCER)	3(3%)	6(4%)	4(3%)	7(5%)	29(22%)	
UNKNOWN	132	93	91	87	91	

p-VALUES FOR TREATMENT COMPARISONS (d):

200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
0.452	0.746	0.605	0.885	0.752	0.877	<0.001	<0.001	<0.001	<0.001

(a) The last observation carried forward approach is used for known ulcer only
(b) Score ranged from 0 (no visible lesions) to 7 (ulcer)
(c) Cochran-Mantel-Haenszel test of overall comparison stratified by baseline status (p-value from Row Mean Scores Differ)
'UNKNOWN' patients were excluded
(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ)
[illegible] patients were excluded

Table 13 (from study 22)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 1 OF 7: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N= 231)		SC-58635 100MG BID (N= 240)		SC-58635 200MG BID (N= 235)		SC-58635 400MG BID (N= 217)		NAPROXEN 500MG BID (N= 225)	
	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCEI
STUDY DAYS										
WK2 (2-28)	64	1	31	1	28	1	28	0	27	8
WK6 (29-76)	32	1	39	1	34	1	35	1	39	5
WK12 (77-91)	95	2	139	7	139	4	122	7	101	23
>91	5	0	5	0	12	0	4	0	6	1
TOTAL	196	4	214	9	213	6	189	8	173	37

Similar to study 021, there was no consistent pattern or relationship between H. pylori and gastric or duodenal ulcer rate or endoscopic score in any of the study groups.

Table 14 (from study 022)

GASTRODUODENAL ENDOSCOPY RESULTS
PART 5 OF 7: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE AS DETERMINED BY BOTH THE FLEXSURE AND CLO TESTS (a)
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N= 231)	SC-58635 100MG BID (N= 240)	SC-58635 200MG BID (N= 235)	SC-58635 400MG BID (N= 217)	NAPROXEN 500MG BID (N= 225)	p-VALUE (c)
WEEK 12 CRUDE ULCER RATE BY H. PYLORI STATUS:						0.049
POSITIVE	4.8% (1/ 21)	14.8% (4/ 27)	3.6% (1/ 28)	11.8% (2/ 17)	38.9% (7/ 18)	
NEGATIVE	5.6% (3/ 54)	5.7% (5/ 88)	3.3% (3/ 92)	4.1% (4/ 97)	25.5% (25/ 98)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)						
	0.932	0.170	0.604	0.267	0.277	

(a) Positive (negative) patients should test positive (negative) by both the Flexsure and CLO tests. In all other cases, the patients are excluded from the H. Pylori effect analysis
(b) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ), patients with unknown endoscopy are excluded
(c) Overall H. Pylori effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by Baseline score and treatment (p-value from Row Mean Scores Differ), patients with unknown endoscopy are excluded

Other historic risk factors such as history of cardiovascular disease, age, NSAID intolerance, history of gastroduodenal ulcer and history of GI bleeding did not reveal any consistent statistical relationship to the gastroduodenal injury.

In the placebo group there was a statistically significant relationship between gastroduodenal ulcers and steroid usage. This relationship was not present in other groups. This is an interesting finding but may simply be due to the baseline low placebo group ulcer rate. The lack of relationship in the other groups sheds little light on the unresolved medical debate regarding the risks of ulcer disease associated with the use of corticosteroids.

Table 15 (from study 022)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7.8 OF 7: COMPARISON OF STEROIDS USE
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=231)	SC-58635 100MG BID (N=240)	SC-58635 200MG BID (N=235)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=225)	p-VALUE (b)
WEEK 12 CRUDE ULCER RATE BY STATUS:						0.345
STEROIDS USE - YES	11.4% (4/ 35)	4.8% (3/ 62)	4.3% (2/ 46)	7.3% (3/ 41)	29.2% (14/ 48)	
STEROIDS USE - NO	0.0% (0/ 64)	7.0% (6/ 86)	4.0% (4/ 99)	5.6% (5/ 89)	24.7% (22/ 89)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.008	0.474	0.796	0.990	0.549	
FINAL CRUDE ULCER RATE BY STATUS:						0.221
STEROIDS USE - YES	5.7% (4/ 70)	3.2% (3/ 95)	2.5% (2/ 79)	4.5% (3/ 66)	22.4% (15/ 67)	
STEROIDS USE - NO	0.0% (0/130)	4.7% (6/128)	2.9% (4/140)	3.8% (5/131)	15.4% (22/143)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.004	0.474	0.897	0.939	0.288	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ)
(b) Overall effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ)

Disease altering drugs did not otherwise show any statistical relationship to ulcer development as shown in table 16.

Table 16 (from study 022)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7.9 OF 7: COMPARISON OF DMARDS USE
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=231)	SC-58635 100MG BID (N=240)	SC-58635 200MG BID (N=235)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=225)	p-VALUE (b)
WEEK 12 CRUDE ULCER RATE BY STATUS:						0.175
DMARDS USE - YES	3.0% (1/ 33)	7.1% (4/ 56)	2.1% (1/ 48)	2.2% (1/ 46)	22.6% (12/ 53)	
DMARDS USE - NO	4.5% (3/ 66)	5.4% (5/ 92)	5.2% (5/ 97)	8.3% (7/ 84)	28.6% (24/ 84)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.837	0.915	0.409	0.236	0.348	
FINAL CRUDE ULCER RATE BY STATUS:						0.189
DMARDS USE - YES	1.4% (1/ 69)	5.1% (4/ 78)	1.3% (1/ 75)	1.6% (1/ 64)	15.6% (12/ 77)	
DMARDS USE - NO	2.3% (3/131)	3.4% (5/145)	3.5% (5/144)	5.3% (7/133)	18.8% (25/133)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.804	0.754	0.328	0.198	0.406	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ)
(b) Overall effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ)

Aspirin usage appeared to have an opposite effect on ulcer rates in placebo compared to the celecoxib group. When reviewed in the light of the other studies in this submission, the data reveals no consistent pattern. And will be discussed later in this review.

Table 17 (from study 22)

TABLE 33
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7.1 OF 7: COMPARISON OF PATIENTS WHO USED ASPIRIN VS. NOT
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=231)	SC-58635 100MG BID (N=240)	SC-58635 200MG BID (N=235)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=225)	p-VALUE (b)
WEEK 12 CRUDE ULCER RATE BY STATUS:						0.155
USE ASPIRIN	0.0% (0/ 9)	0.0% (0/ 16)	13.3% (2/ 15)	11.1% (1/ 9)	0.0% (0/ 9)	
NOT USE ASPIRIN	4.4% (4/ 90)	6.8% (9/132)	3.1% (4/130)	5.8% (7/121)	28.1% (36/128)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.448	0.274	0.229	0.920	0.066	
FINAL CRUDE ULCER RATE BY STATUS:						0.125
USE ASPIRIN	0.0% (0/ 16)	0.0% (0/ 23)	9.5% (2/ 21)	6.7% (1/ 15)	0.0% (0/ 16)	
NOT USE ASPIRIN	2.2% (4/184)	4.5% (9/200)	2.0% (4/198)	3.8% (7/182)	19.1% (37/194)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE(a)	0.456	0.287	0.159	0.866	0.047	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ)
(b) Overall effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ)

v. Summary: In this 12 week study of Rheumatoid Arthritis patients celecoxib at all dosage regimens was associated with a statistically significant and clinically meaningful lower ulcer incidence than naproxen. The ulcer rate was higher in all celecoxib groups than the placebo group. These differences were not statistically significant. The study was powered to show statistical differences between celecoxib and naproxen, not to compare placebo to celecoxib. The ulcer rate in Rheumatoid Arthritis patients in all groups in this review was similar to the rate seen in Osteoarthritis patients under similar experimental conditions in study 021. This similarity again suggests a lack of meaningful risk associated with the use of DMARDs and corticosteroids in these patients. The potential relationship between ulcer risk and low dose aspirin will be a clinically important issue and will be discussed later in this review.

D. Study 071: A Multicenter, double-blind, parallel group study comparing the incidence of gastroduodenal ulcer associated with celecoxib 200mg b.i.d. with that of diclofenac 75mg b.i.d. and ibuprofen 800mg t.i.d. taken for 12 weeks in patients with Osteoarthritis or Rheumatoid Arthritis

1. Study objectives (from the text of study 071)

Primary Objective

The primary objective of this study was to compare the cumulative (up to12 weeks) incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

Secondary Objectives

The secondary objectives of this study were to:

a. Compare the short-term safety and tolerability of celecoxib 200 Mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA;
b. Evaluate the effect of Helicobacter pylori (H. pylori) status on the Development of gastroduodenal ulcers;
c. Compare the effect of celecoxib versus diclofenac and ibuprofen on Quality of Life (QOL); and
d. Compare the arthritis efficacy of celecoxib 200 mg BID with that of diclofenac75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

2. Study design: The study did not include a placebo group. It did include serial endoscopies at baseline and weeks 4, 8, and 12. Unless stated otherwise methods were similar to studies 021and 022 inclusion and exclusion criteria were not identical to the previous studies and are listed in table 19.

Table 18 (reviewer's table)

Inclusion Criteria	Exclusion Criteria
1. Been of legal age and consent: 2. If female and of childbearing potential, been using adequate contraception, not been lactating and had a negative serum pregnancy test within seven days before the first dose of study medication : 3. Had a documented history of OA or RA of at least three months duration: 4. Had a functional capacity classification of I-III at the baseline visit: 5. Required chronic NSAID therapy in the opinion of the investigator: 6. Provided written informed consent:	1. Had been diagnosed with any other inflammatory arthritis or active gout: 2. Had an active malignancy of any type: 3. Had been diagnosed with or had been treated for esophageal, gastric Pyloric channel, or duodenal ulceration within 30 days before receiving the first dose of study medication: 4. Had active GI disease(e.g. inflammatory bowel disease or Barrett's esophagus: 5. Had received grater than or equal to 150 mg/day diclofenac or 2400 mg/day ibuprofen daily for arthritis during the 30 days prior to the first dose of study medication. Lesser doses for less than 5days/week were allowed: 7. Had an esophageal, gastric, pyloric channel or duodenal ulcer at screening endoscopy: 8. Had a history of gastric or duodenal surgery other than simple oversew: 9. Had acute or chronic renal failure Hepatic disease, or a coagulation disorder:

	10. Had a clinically significant abnormal screening ECG **11. had abnormal screening lab considered to be clinically significant by the investigator:** **12. Had a known hyypersensitivity to COX-2 inhibitors, sulfonamides or NSAIDs:** **13. Had received or was scheduled to receive any other investigational drug during the course of the study:** **14. Had previously been admitted to this study**

The same protocol changes noted in the review of study 021applied to studies 071and 062 . Prohibited medications during the study included NSAIDs other than study medication (low dose aspirin equal to or less than 325 mg/day could be continued at the same dose regimen during the study), anti-ulcer therapy, antibiotics used as therapy for H. pylori, anticoagulants, anti-acids and antineoplastics (other than azathioprine or methotrexate used for RA patients).

Blinding was apparently accomplished despite the difference in dosing regimen between ibuprofen and the other comparators. This meant including placebo tablets for all groups except for those receiving ibuprofen so as to have a t.i.d. regimen for all patients. This did produce a different dosage interval than other protocols. Both studies 071 and 062 included endoscopy at 0,4,8 and 12 weeks. This approach differs from the other 3 endoscopic studies and was intended to define the risk over time of ulcers in the population groups studied. Endoscopic criteria and were similar to those used in studies 021 and 022.

3. Results:

i. Patient demographics: Treatment groups were comparable with respect to age, gender, race, history of GI bleeding, gastroduodenal ulcer, cardiovascular disease and NSAID intolerance.

Baseline endoscopy scores were comparable, as was H. pylori serology. Alcohol usage was only ascertained in the medical history as the presence or absence of alcoholism. It is generally accepted that alcohol intake is historically underestimated. This study likely underestimated alcohol intake even further with the form of information ascertainment. Tobacco and alcohol use was not part of the initial demographic analysis by the sponsor. At the request of the reviewer, the sponsor did an analysis of alcohol and tobacco intake, individually and combined by treatment group for both studies 071 and 062. The distribution of alcoholism and tobacco use was similar between the three study groups. The data are presented in table 16. Although there may be a slight confounding effect of alcohol it's use is equally divided among the groups and is not felt to represent a potential bias in this study.

Table 19

Cumulative 12 week ulcer rates	No alcoholism or tobacco use.	Alcoholism without tobacco use	No alcoholism Tobacco use	Alcoholism and tobacco use
Celecoxib	19/273 (7%)	¼ (20%)	5/78 (6%)	0/10 (0%)
Diclofenac	27/283 (11%)	1/12 (8%)	8/74 (11%)	0/8 (0%)
Ibuprofen	56/269 (22%)	2/7 (29%)	17/69 (25)	3/9 (33%)

ii. **Patient disposition:** A total of 1099 patients were randomized. The target enrollment of 720was exceeded by 66%. The stated reason was "because of an unexpectedly large enrollment immediately prior to the last enrollment day. At the request of the reviewing staff, an analysis of the UGI parameters for the first 720 enrolled patients was performed by the

sponsor and revealed no meaningful difference from the larger enrollment analysis, .366, 387 and 346 patients were enrolled into the Celebrex, diclofenac and ibuprofen groups respectively. Twelve-week evaluability data were available for 75% of celecoxib patients, 72% of diclofenac and 60% of ibuprofen participants.

iii. Serious GI adverse events

The sponsor noted three clinically significant UGI events, one in each study group . This reviewer felt that only two cases warranted this definition. Case (US0381-3537), in a celecoxib patient resulted in clinical bleeding (weakness, dizziness, black stool and an 8 point drop in hematocrit) and the patient was withdrawn from the study. This patient was 82 years old,S/P MI with a history of GI bleeding and gastroduodenal ulcers! The other two cases (US0341-1280: on diclofenac and US0336-1272: on ibuprofen) involved less significant drop in hematocrit and no symptoms or clinical signs of bleeding. Patient US 0336-1272 was withdrawn from the study at the time of routine scheduled endoscopy due to the presence of an active ulcer. Although the endoscopic description reported a bleeding ulcer, no stool for occult blood was performed and there was only a 1 point drop in hematocrit. This 77 year old patient had a vague cardiac history and a history of gastroduodenal ulcer . CRF medical history stated that the patient had undergone a cardiac catheterization in the past. This patient was on no cardiac medications. His baseline ECG did reveal poor R wave progression anteriorly which is suggestive of a prior MI. This patient did not have true clinical signs of bleeding but he did meet the criteria of "significant UGI event" as defined in the protocols.

The third patient did not meet the definition of a clinically significant UGI event. The narrative provided by the sponsor appears below.

Patient No. US 0341-1280 (Hematocrit Decrease, Duodenitis Erosive, Gastritis Erosive) was a 49 year old female with a history of right lung emphysema and osteoarthritis. At Baseline, the patient's hematocrit was 44.0%. H. pylori was negative. Endoscopy completed the following day, showed multiple erosions in the antrum with at least 40 punctate bleeding points in the antrum and corpus of the stomach. That same day, the patient was randomized for enrollment and received diclofenac 75 mg BID. The Week 4 endoscopy was performed 22 days later and revealed a 3 cm hiatal hernia, gastritis in the body and antrum of the stomach and 40-50 petechial lesions in the stomach with one erosion measuring 2 mm and containing a small clot. There were two antral erosions measuring 3-5 mm. Three shallow, superficial "ulcers," up to 6 mm in diameter, were noted in the bulb of the duodenum. No bleeding was noted. According to the endoscopist, these lesions had more depth to them than erosions but they were not deep lesions. The Investigator felt these lesions were actually erosions, and not ulcers, because they had no measurable depth. The hematocrit that day was 41.0%. The patient had no abdominal pain, melena, hematemesis or other symptoms of gastrointestinal bleeding. Stools for guaiac were not obtained. The Week 8 endoscopy, completed 28 days later, was negative except for 11-25 gastric petechiae. The patient had one episode of indigestion, which she treated with a single dose of calcium carbonate. The Week 12 endoscopy, completed 29 days after previous endoscopy, revealed 10 petechiae in the antrum of the stomach. An 8 mm AV malformation was also noted in the second portion of the duodenum. CLOtest was negative. Hematocrit that same day was 37.0%. The patient completed the study and no further follow-up was done. Concomitant medications included multivitamins. The patient has recovered. The Investigator was uncertain whether this event was related to study medication. This event was considered a clinically significant GI event by the independent GI events committee.

This patient had multiple erosions and "at least 40 punctate bleeding points" at baseline. These findings did not exclude the patient from the study and she was randomized. Baseline hematocrit was 44%. Routine week 4 endoscopy was performed early on day 22. It revealed two antral erosions, one of which was defined as 2mm in size "with a clot" as well as 3 shallow duodenal ulcers. Hematocrit at that time was 41%. The patient was mistakenly not withdrawn from the study. At week 8 and final week 12 endoscopies spontaneous healing of the ulcers and erosions was noted. Routine hematocrit done at the conclusion of the study was 37%. There was never clinical evidence of bleeding and no stool for occult blood was tested. The only basis for considering this case to be a clinically significant UGI event is the fall in hematocrit over the course of twelve weeks. Without evidence of bleeding associated with the fall from 41% to 37% over the final 4 weeks of the study, this does not meet criteria for the definition of a clinically significant UGI event. The significant fall in hemoglobin occurred after the patients ulcers and erosions had spontaneously healed. The 4-week endoscopy note appears below. A subsequent letter from the endoscopist, which was forwarded to the sponsor also, appears below. I t is unclear whether he was suggesting that the lesions be reclassified. The case was counted as an ulcer, which appears appropriate, based on the original 4-week endoscopy report. This case did not appear to warrant a classification of clinically significant UGI event.

APPEARS THIS WAY
ON ORIGINAL

[redacted]

1049-9-7-02-071

GASTROENTEROLOGY

12/22/97

[redacted] (# 1280 NIM)

Re: [redacted]

The week 4 endoscopy performed on Oct 21, 1997 showed 3 antral erosions (very superficial breaks in mucosa up to 5 mm in size. In the duodenal bulb there were 3 superficial ulcers up to 6 mm in diameter. These lesions had more depth to them as I would not call them erosions, but these were not deep lesions. This may be more a semantic issue than a substantive one as I believe erosions represent the earliest form of an ulcer & that they represent "mini" ulcers.

Sincerely,

[redacted]

APPEARS THIS WAY
ON ORIGINAL

DRAFT

APPEARS THIS WAY
ON ORIGINAL

#1280
MIM 196

[redacted]

PATIENT NAME [redacted] MIM 1280 PATIENT ID #: 58803
DATE: 10/22/97

PROCEDURE: Esophagogastroduodenoscopy, Diagnostic

INDICATIONS FOR PROCEDURE: The patient is a 49 year old female here for a esophagogastroduodenoscopy to evaluate protocol.

MEDICATIONS: Fentanyl 100 micrograms IV, Versed 2 mg IV, Cetacaine Spray
ADMINISTERED BY: Sidney J. Malawer, M.D.
MONITORS: O2, EP, and Cardiac

PROCEDURE: After obtaining routine informed consent, the patient was brought into the procedure room, where the monitoring equipment was attached, intravenous sedation was administered. The Pentax EG-2730 gastroscope was introduced through the mouth and advanced to the second portion of the duodenum. The endoscope was withdrawn as the mucosa was carefully inspected.

FINDINGS: The esophagus and esophagogastric-junction was completely normal in appearance. A hiatal hernia was found below the gastroesophageal junction. It was non-inflamed. It was 3 cm in size. It was found 37 cm from the point of entry. Photo-documentation was obtained. Gastritis was found in the body and the antrum of the stomach. Gastric juice was aspirated and had a Ph of 2.5 There are multiple petechial lesions in the stomach (40-50) with one erosion measuring 2 mm. and containing a small clot. Two antral erosions measuring 3-5 mm. in size are present. Multiple ulcers were found in the bulb of the duodenum. Three shallow ulcers are present in the bulb measuring up to 6 mm. in diameter. None are bleeding. The scope was then completely withdrawn from the patient and the procedure terminated.

COMPLICATIONS: None

POST-OP DIAGNOSIS: 1) Normal esophagus
2) 3 cm hiatal hernia below the gastroesophageal junction
3) Gastritis in the body and the antrum of the stomach
4) Ulcers, multiple in the bulb of duodenum

RECOMMENDATIONS:

REPEAT EXAM: as per protocol

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Of note is that both of the accurately reported clinically significant UGI events occurred in patients with multiple risk factors for NSAID related gastroduodenal ulcers.

iv. Endoscopy Results:

Endoscopic validation:

A total of 933 endoscopy reports were reviewed. This represented 460/1099 patients enrolled in the study. 24 or 5% of patients had inadequate endoscopic information on the primary source document, the endoscopy report. This required a decision to censor these data or extrapolate from a qualitative description of erosion number (few, several, many etc.) to the required numerical quantitation. The sponsor chose to extrapolate the data, which introduces an error factor. This is not felt to change the overall clinical meaning of

the study conclusions and is unlikely to even change the gastric scoring data significantly. It does represent a flaw in data collection that should be addressed in future studies by the sponsor.

iv. Endoscopy

Crude gastroduodenal ulcer rate by interval is seen in table 20 and ulcer rates based on survival analysis are seen in table 21. At all intervals ibuprofen is associated with a statistically higher incidence of ulcers that diclofenac and celecoxib. In all intervals celecoxib and diclofenac are statistically comparable.
Of note is that the celecoxib final or cumulative ulcer rate is 7%, slightly higher than in studies 021 and 022 and higher than placebo in these studies. These are not analogous studies because of the multiple endoscopies at 4-week intervals in this study that detected asymptomatic ulcers. Asymptomatic ulcers occurring in studies 021 and 022 may have healed spontaneously during the course of the study. It is therefore difficult to compare ulcer rates in this study to placebo ulcer rates in study 021 and 022. The ulcer rates in each interval, however, were higher than the final ulcer rates in the placebo groups from studies 021 and 022. The final ulcer rate for the diclofenac group of 10% is less than the 15% rate seen in the other study using this comparator (041). In study 041 there was no baseline endoscopy to define clearly the incidence of new ulcers. These patients were on NSAIDs up to the study date and certainly some patients entered the study with pre-existing ulcers. There were no routine interim endoscopies to detect the presence of ulcers similar to the design of 071. The differences between the to studies is too great to consider the diclofenac data from 041 when analyzing study 071.

Table 20 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 2 OF 8: ANALYSIS OF CRUDE ULCER RATE

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 365)	DICLOFENAC 75MG BID [N= 387]	IBUPROFEN 800MG TID (N= 345)	OVERALL p-VALUE (a)	SC-58635 VS DICLOFENAC p-VALUE (c)	SC-58635 VS IBUPROFEN p-VALUE [c]	DICLOFENAC VS IBUPROFEN p-VALUE (c)
WEEK 0-4							
CRUDE ULCER RATE (a)				<0.001	0.370	<0.001	<0.001
NO ULCER	334 (94%)	333 (95%)	281 (87%)				
ULCER	13 (4%)	18 (5%)	43 (13%)				
UNKNOWN [WITHOUT & WITH ENDO)	38 (19/ 9)	37 (25/12)	22 (15/ 7)				
WEEK 0-8							
CRUDE ULCER RATE (a)				<0.001	0.220	<0.001	<0.001
NO ULCER	289 (94%)	296 (91%)	226 (80%)				
ULCER	20 (6%)	28 (9%)	57 (20%)				
UNKNOWN [WITHOUT & WITH ENDO)	56 (9/47)	63 (15/48)	62 (12/50)				
WEEK 0-12							
CRUDE ULCER RATE (a)				<0.001	0.138	<0.001	<0.001
NO ULCER	269 (91%)	270 (88%)	198 (72%)				
ULCER	25 (9%)	36 (12%)	78 (28%)				
UNKNOWN [WITHOUT & WITH ENDO)	71 (9/62)	81 (15/66)	69 (11/58)				
WEEK 0-FINAL (b)							
CRUDE ULCER RATE (a)				<0.001	0.123	<0.001	<0.001
NO ULCER	331 (93%)	336 (90%)	256 (77%)				
ULCER	25 (7%)	36 (10%)	78 (23%)				
UNKNOWN [WITHOUT & WITH ENDO)	9 (9/ 0)	15 (15/ 0)	11 (11/ 0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) Based on the final endoscopy result of each patient.
(c) Cochran-Mantal-Haenszel test of treatment comparison for known ulcer vs. non-ulcer stratified by baseline acute

Table 21 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 4 OF 8: CUMULATIVE ULCER RATE BASED ON KAPLAN-MEIER ESTIMATES AND GROUPED SURVIVAL ANALYSIS

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 365)	DICLOFENAC 75MG BID (N= 387)	IBUPROFEN 800MG TID (N= 345)	OVERALL p-VALUE (a)	SC-58635 VS DICLOFENAC p-VALUE (a)	SC-58635 VS IBUPROFEN p-VALUE (a)	DICLOFENAC VS IBUPROFEN p-VALUE (a)
RATE BASED ON KAPLAN-MEIER ESTIMATES (b), p-VALUE FROM LOG-RANK TEST							
WEEK 4 (0-35 DAYS)	3.9%	5.2%	13.3%	<0.001	0.497	<0.001	<0.001
WEEK 8 (0-63 DAYS)	6.1%	8.3%	18.5%	<0.001	0.280	<0.001	<0.001
WEEK 12 (0-91 DAYS)	8.7%	13.8%	41.9%	<0.001	0.189	<0.001	<0.001
RATE AND p-VALUE BASED ON GROUPED SURVIVAL ANALYSIS (c)							
WEEK 4 (0-35 DAYS)	3.8%	5.1%	13.3%	<0.001	0.453	<0.001	<0.001
WEEK 8 (0-63 DAYS)	6.1%	8.1%	18.5%	<0.001	0.318	<0.001	<0.001
WEEK 12 (0-91 DAYS)	9.2%	13.0%	32.2%	<0.001	0.295	<0.001	<0.001

(a) The p-values were based on the data from the periods of 0-35, 0-63, and 0-91 days, respectively. Patients with an endoscopy beyond the specific period were censored at the end of the period.
(b) The rates were read at the time points right after days 35/63/91 from the Kaplan-Meier curve based on all data from the study.
(c) Mantel-Cox test was used based on known ulcers and known no ulcers; see Categorical Data Analysis Using the SAS System, M. Stokes, C. Davis, and G. Koch, 1995, p.465-471.

The breakdown of ulcer data by disease seen in table 22 reveals an interesting phenomenon. Across all intervals in the diclofenac group there is a statistically significant higher ulcer rate in the Osteoarthritis group compared to the Rheumatoid Arthritis group. This same pattern was seen to a much smaller extent in two out of the three intervals in the ibuprofen group. The pattern was flipped in the celecoxib group but was not statistically significant. These data will be reviewed again in the analysis of study 062 to look for confirmatory patterns.

Table 22 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7 OF 8: COMPARISON OF DISEASE STATUS (OA VS RA) WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		SC-58635 200MG BID (N= 365)	DICLOFENAC 75MG BID (N= 387)	IBUPROFEN 800MG TID (N= 345)	p-VALUE (b)
WEEK 0-4	CRUDE ULCER RATE BY DISEASE CATEGORY				0.300
	OA	3.2% (8/252)	6.6% (17/258)	13.5% (32/237)	
	RA	5.9% (5/ 85)	1.1% (1/ 92)	11.6% (10/ 86)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.212	0.030	0.557	
WEEK 0-8	CRUDE ULCER RATE BY DISEASE CATEGORY				0.099
	OA	6.0% (14/235)	10.8% (26/240)	21.1% (43/204)	
	RA	8.1% (6/ 74)	2.4% (2/ 84)	17.7% (14/ 79)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.434	0.010	0.392	
WEEK 0-12	CRUDE ULCER RATE BY DISEASE CATEGORY				0.606
	OA	7.2% (16/223)	14.1% (32/227)	27.9% (56/201)	
	RA	12.7% (9/ 71)	5.1% (4/ 79)	29.3% (22/ 75)	
	p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.117	0.016	0.915	

(a) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.
(b) Overall disease effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by baseline score and treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.

Stratification for the use of low dose aspirin did not reveal concomitant use as a risk factor at any interval for any group except the12-week ulcer rate for diclofenac. The lack of uniform data across these various studies is of interest to this reviewer. These studies in

composite do not support or negate the potential risks of low dose aspirin when used concomitantly with NSAIDs. It may be speculated that the biologic effect of different NSAIDs varies enough to yield biologically different interactions between aspirin and the individual NSAIDs. Theories regarding the potential beneficial healing effects of cox-2 activity in ulcer healing may also play a role in these studies findings.

Table 23 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 8.1 OF 8: COMPARISON OF ASPIRIN USE WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		SC-58635 200MG BID (N= 365)	DICLOFENAC 75MG BID (N= 387)	IBUPROFEN 800MG TID (N= 345)	P-VALUE (b)
WEEK 0-4	CRUDE ULCER RATE BY STATUS				0.974
	USED ASPIRIN	2.5% (1/ 40)	8.1% (3/ 37)	11.1% (5/ 45)	
	DID NOT USE ASPIRIN	4.0% (12/297)	4.8% (15/313)	13.3% (37/278)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.568	0.408	0.879	
WEEK 0-8	CRUDE ULCER RATE BY STATUS				0.728
	USED ASPIRIN	5.3% (2/ 38)	14.3% (5/ 35)	19.5% (8/ 41)	
	DID NOT USE ASPIRIN	6.6% (18/271)	8.0% (23/289)	20.2% (49/242)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.678	0.159	0.846	
WEEK 0-12	CRUDE ULCER RATE BY STATUS				0.311
	USED ASPIRIN	5.6% (2/ 36)	25.0% (8/ 32)	29.3% (12/ 41)	
	DID NOT USE ASPIRIN	8.9% (23/258)	10.2% (28/274)	28.1% (66/235)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.462	0.011	0.875	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ.)
(b) Overall subgroup effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ.)

Steroid and DMARD use were analyzed as variables and did reveal interesting effect. The data on steroid usage shows a trend towards higher ulcer risk in the celecoxib group. DMARD usage shows a statistically significant association with treatment related ulcers in 2 of 3 intervals in the celecoxib category and only 1 of 6 intervals in the active comparators. This relationship was not seen in study 022 or 062. The number of ulcers and the number of patients using DMARDs were small. Definitive statements regarding the effects of DMARDs on NSAID and celecoxib related ulcers are not possible with inconsistent results as noted.

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Table 24 (from study 071)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 8.9 OF 8: COMPARISON OF UNARD USE STATUS
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		SC-58635 200MG BID (N= 365)	DICLOFENAC 75MG BID (N= 387)	IBUPROFEN 800MG TID (N= 345)	P-VALUE (b)
WEEK 0-4	CRUDE ULCER RATE BY STATUS				0.483
	CURRENT UNARD USE - YES	9.3% (4/ 43)	2.1% (1/ 48)	16.3% (8/ 49)	
	CURRENT UNARD USE - NO	3.1% (9/294)	5.6% (17/302)	12.4% (34/274)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.048	0.259	0.541	
WEEK 0-8	CRUDE ULCER RATE BY STATUS				0.684
	CURRENT UNARD USE - YES	15.2% (5/ 33)	4.4% (2/ 45)	23.3% (10/ 43)	
	CURRENT UNARD USE - NO	5.4% (15/276)	9.3% (26/279)	19.6% (47/240)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.035	0.204	0.752	
WEEK 0-12	CRUDE ULCER RATE BY STATUS				0.625
	CURRENT UNARD USE - YES	15.6% (5/ 32)	4.8% (2/ 42)	27.9% (12/ 43)	
	CURRENT UNARD USE - NO	7.6% (20/262)	12.9% (34/264)	28.3% (66/233)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.160	0.977	0.845	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ.)
(b) Overall subgroup effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ.)

H. pylori data using serologic methodology at the baseline as well as CLO test and histology at the conclusion revealed no relationship to NSAID related ulcers. Past history of gastroduodenal ulcer and gi bleeding did correlate with higher ulcer rates in celecoxib NSAID users.

v. Reviewers Summary:

Study 071 revealed a statistically significant lower ulcer incidence in celecoxib treated patients compared to ibuprofen treated patients. There was no statistically significant difference in ulcer incidence between celecoxib and diclofenac treated patients. The highest ulcer incidence occurred in the first 4 weeks of treatment within each group, although celecoxib and ibuprofen new ulcer rates increased in the 8- 12 week interval compared to the 4-8 week interval. Clinically significant UGI adverse events occurred in two patients; one in the celecoxib group and one in the ibuprofen group. Comparisons with studies 021 and 022 are of limited value due to significant differences in study design.

E. Study 062: A multicenter, double-blind, parallel group study comparing the incidence of gastroduodenal ulcer associated with celecoxib 200mg b.i.d. with that of naproxen 500mg b.i.d. taken for 12 weeks in patients with Osteoarthritis and Rheumatoid Arthritis.

1. STUDY OBJECTIVES (from the text of study 062)

Primary Objective

The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcer associated with celecoxib 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA.

Secondary Objectives

The secondary objectives of this study were to:

1. Compare the short-term safety and tolerability of celecoxib 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA;

2. Evaluate the effect of Helicobacter pylori (H. pylori) status on the development of gastroduodenal ulcers;
3. Compare the effect of celecoxib versus naproxen on quality of life; and
4. Compare the arthritis efficacy of celecoxib 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA.

2. Study design:

The design was similar to study 071 except for the change in comparators, from diclofenac and ibuprofen to naproxen and a change in the exclusion criteria such that an abnormal ECG was no longer mentioned. Unlike study 071, blinding did not require the addition of a third dose a day since both compounds were administered b.i.d.

3. Results:

i. Demographics: Treatment groups were comparable for age, race, gender, H. pylori serologic status, as well as history of GI bleeding, NSAID GI intolerance and cardiovascular disease. Baseline endoscopy scores were comparable as well, including serologic testing for H. pylori antibodies. Data on baseline distribution of alcohol and tobacco use were not initially included in the analysis. At the reviewers request the sponsor broke down the ulcer data within each study group based on these possible confounding variables. The treatment groups for study 062 were similar in terms of tobacco use. There was a twofold differential between the groups in terms of alcoholism. The celecoxib group had a 10/267 or 4% rate of alcoholism. The naproxen group had a 5/265 or 2% alcoholism rate. Although table 26 suggests a possible confounding effect of alcohol use on naproxen related ulcers (the celecoxib group was too small for comment), the small number of patients in this category was felt by this reviewer and a project statistician to obviate concern over any possible bias associated with the differing alcoholism rates between the two study groups.

ii. Patient disposition:
A total of 537 patients were randomized, 34% over the initial statistically defined population to be enrolled. At the reviewing teams' request, the sponsor analyzed the data on intended study population size. No difference in results was noted. 73% of celecoxib and 53% of naproxen patients were evaluable at week 12. The disparity was partially so large because so many patients in the naproxen were withdrawn from the study early due to adverse events and ulcers found at earlier endoscopies (68 patients).

Table 25

Cumulative 12 week ulcer rates	No alcoholism or tobacco use.	Alcoholism without tobacco use	No alcoholism Tobacco use	Alcoholism and tobacco use
Celecoxib	7% (14/214)	0% (0/3)	12% (6/50)	0% (0/2)
Naproxen	35% (74/209)	87% (5/6)	19% (9/48)	25% (1/4)

iii. Serious UGI events:
The sponsor noted two clinically significant UGI events, (gastric outlet obstruction associated with an acute ulcer and anemia and heme positive stool associated with an ulcer) both in the naproxen group. The case reports are reproduced below.

(Study 062 Text)
Patient No. US0230-45313086 DER No. 970903-CL984 (Intestinal Obstruction) was a 59 year old female with a history of high cholesterol, right knee surgery, kidney stones, stomach stapling, total abdominal hysterectomy, chronic gastritis, and OA. The patient was enrolled into the study on 19 June 1997 and randomized to receive naproxen 500 mg BID. After 60 days of treatment, a pyloric channel ulcer was detected during her routine Week 8 endoscopy. Study medication was discontinued and the patient was withdrawn from the study. She was started on lansoprazole. Two days later, the patient complained of nausea. Five days after that, she noted blood in her stool. A rectal exam revealed a probable hemorrhoid but no obvious bleeding. The hemoglobin was 14.1 with a hematocrit of 45.0 compared to a hemoglobin of 11.8 and hematocrit of 40.0 five days earlier at the Week 8 Visit. The patient was sent home with guaiac cards. Lansoprazole was discontinued and the patient was started on famotidine and promethazine. suppositories. That same evening, the patient called the doctor's office with complaints of nausea, vomiting and burning epigastric substernal chest pain. Evaluation demonstrated a blood pressure of 110/90 supine, falling to 102/60 standing. She also had a urine dipstick which demonstrated a high specific gravity of 1.030 and 4+ ketones. She was admitted to the hospital for dehydration and further evaluation. Intravenous fluids were given for rehydration. An upper GI and small bowel series done two days after hospital admission revealed possible left sided kidney stones and possible gastritis with no definite mass of gastric ulcer. No small bowel abnormality was noted. An upper endoscopy was performed the following day and showed a narrowing of the pylorus secondary to a healing ulcer. There was also a large leathery fruit approximately the size of a fig which was blocking the pyloric channel. This was removed and the patient became asymptomatic. The patient was discharged from the hospital the next day.

Concomitant medications included lovastatin and conjugated estrogens. The patient recovered. Both the Investigator and the Searle Medical Monitor considered this patient's event to be of possible relationship to study medication. This event was considered a clinically significant GI event by the independent GI Events Committee.

Patient No. US0214-61761397 (gastric ulcer, duodenal ulcer) was a 69 year old female with a history of allergic rhinitis, cataract surgery, tonsillectomy, glaucoma, chronic sinusitis, deep vein thrombosis, hypertension, chronic obstructive pulmonary disease, pulmonary fibrosis, nocturnal myoclonus, dysphagia, hiatal hernia, lower esophageal ring, gastroesophageal reflux disease, gastric ulcer, erosive gastritis, irritable bowel syndrome, colon polyp, diverticulosis, chronic diarrhea, appendectomy, colon polypectomy, post-menopausal, lumbar sacral joint disease, basal cell carcinoma removed, iron deficient anemia, allergy to shellfish, multiple drug allergies, and osteoarthritis. She was randomized to receive naproxen 500 mg BID. One week prior to entering this study the patient went to the emergency room complaining of nausea and flu-like symptoms and was treated with ciprofloxacin. Eight days later the patient complained of nausea after receiving the first dose of study medication. An endoscopy performed eleven days later revealed Grade O esophagitis; hiatal hernia with a small paraesophageal component; erosive gastritis in the base of the hernia and into the high body of the stomach with a 1 cm gastric ulcer; 8 erosions in the body of the stomach; and an 8 mm duodenal ulcer onthe anterior wall superior aspect of the cap with 5 duodenal erosions. There was no evidence of active bleeding. Stool was hemoccult positive. The patient's blood pressurewas normal and the patient was asymptomatic so postural measurements were not done. The patient was started on lansoprazole. Study medication was discontinued and the patient terminated from the study. At screening the patient had a positive H. pylori and a hematocrit of 45. Subsequent hematocrit values were 31 and 34, eight and 11 days after starting study medication, respectively.

Concomitant medications included dipivefrin, nicardipine, clonazepam, polysaccharide-iron complex, albuterol, beclomethasone dipropionate, loperamide, and acetaminophen. The patient has recovered. The Investigator determined that this event was probably related to study medication; the Searle Medical Monitor determined that the event was related. (end of Study 062 test)

One patient death unrelated to study medication occurred during the study. A patient in the naproxen group died of a brain stem infarct.

iv. Endoscopic results:

The table 26 reveals a clear and statistically significant difference between groups in terms of gastroduodenal ulcer rate across each time interval and cumulative final ulcer rates. Separate analysis of gastric versus duodenal location gave similar results. Although there was no placebo group, the celecoxib group ulcer rate is higher than controls and more significantly, these rates in each interval is higher than the final placebo rates in the two placebo controlled studies in this submission (021 and 022).

Table 26 (from study 062)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 2 OF 8: ANALYSIS OF CRUDE ULCER RATE

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 269)	NAPROXEN 500MG BID (N= 267)	p-VALUE (c)
WEEK 0-4			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	242 (96%)	200 (81%)	
ULCER	10 (4%)	47 (19%)	
UNKNOWN (WITHOUT & WITH ENDO)	17 (5/12)	20 (14/ 6)	
WEEK 0-8			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	222 (94%)	156 (68%)	
ULCER	15 (6%)	73 (32%)	
UNKNOWN (WITHOUT & WITH ENDO)	32 (3/29)	38 (10/28)	
WEEK 0-12			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	193 (91%)	127 (59%)	
ULCER	18 (9%)	87 (41%)	
UNKNOWN (WITHOUT & WITH ENDO)	58 (3/55)	53 (10/43)	
WEEK 0-FINAL (b)			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	246 (92%)	168 (65%)	
ULCER	20 (8%)	89 (35%)	
UNKNOWN (WITHOUT & WITH ENDO)	3 (3/ 0)	10 (10/ 0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) Based on the final endoscopy result of each patient.
(c) Cochran-Mantel-Haenszel test of treatment comparison for known ulcer vs. Non-ulcer stratified by baseline score

H.pylori status was analyzed by histology and CLOtest. These results were quite different than other studies that used concordance of serology and CLOtest. In the other studies no relationship was consistently found between H.pylori status and ulcer incidence (intra or intergroup). In this study there was a statistically significant association between ulcer development and the presence of H. Pylori infection in the celecoxib group at week 4 and week 12. A strong trend was seen at week 8. A striking lack of correlation in the naproxen group was seen where ulcers had no relationship to H.pylori status. It is unclear whether this is a biologic phenomenon or whether the risk of ulcers associated with naproxen alone was so high, as to overwhelm any smaller risk associated with H. pylori in this relatively small trial. The lack of association in other studies however cannot be ignored.

Table 27 (from study 62)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 5 OF 8: COMPARISON OF H. PYLORI POSITIVE VS. H. PYLORI NEGATIVE AS DETERMINED BY THE BIOPSY AND CLO TESTS (a)
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 269)	NAPROXEN 500MG BID (N= 267)	p-VALUE (c)
WEEK 0-4 CRUDE ULCER RATE BY H. PYLORI STATUS			0.341
POSITIVE	5.9% (2/ 34)	7.1% (2/ 28)	
NEGATIVE	0.7% (1/149)	7.8% (9/116)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.036	0.921	
WEEK 0-8 CRUDE ULCER RATE BY H. PYLORI STATUS			0.110
POSITIVE	9.4% (3/ 32)	25.9% (7/ 27)	
NEGATIVE	2.8% (4/145)	19.5% (22/113)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.094	0.372	
WEEK 0-12 CRUDE ULCER RATE BY H. PYLORI STATUS			0.165
POSITIVE	12.9% (4/ 31)	29.6% (8/ 27)	
NEGATIVE	2.9% (4/136)	30.2% (32/106)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (b)	0.023	0.675	

(a) If both tests are positive (negative), then the patient is classified as positive (negative). Otherwise, the patient is not included in this analysis.
(b) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.
(c) Overall H. Pylori effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by baseline score and treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.

Table 27 compares ulcer rates by underlying disease. There was no statistical difference in ulcer incidence between RA and OA groups. There was a trend towards higher ulcer rates in the OA patients compared to the RA patients in the naproxen group but not in the celecoxib group. These data are consistent with data from study 071 described previously. Interstudy comparison between studies 021 and 022 revealed little difference in final gastroduodenal ulcer rates between the two types of arthritic populations in active comparator and celecoxib groups. These data lend strong support to the concept that NSAIDs at a minimum do not have a worse safety profile in RA patients compared to OA patients. Due to the lack of power of these studies, the trends may or may not be reflective of a truly higher risk of NSAID related ulcers in Osteoarthritis compared to Rheumatoid Arthritis.

Table 28 (from study 062

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 7 OF 8: COMPARISON OF DISEASE STATUS (OA VS RA)
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

	SC-58635 200MG BID (N= 269)	NAPROXEN 500MG BID (N= 267)	p-VALUE (b)
WEEK 0-4 CRUDE ULCER RATE BY DISEASE CATEGORY			0.297
OA	4.5% (8/179)	20.7% (37/179)	
RA	2.7% (2/ 73)	14.7% (10/ 68)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.466	0.428	
WEEK 0-8 CRUDE ULCER RATE BY DISEASE CATEGORY			0.285
OA	6.6% (11/166)	34.3% (57/166)	
RA	5.6% (4/ 71)	25.4% (16/ 63)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.623	0.342	
WEEK 0-12 CRUDE ULCER RATE BY DISEASE CATEGORY			0.125
OA	8.4% (13/154)	45.2% (70/155)	
RA	8.8% (5/ 57)	28.8% (17/ 59)	
p-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	0.977	0.079	

(a) From Cochran-Mantel-Haenszel test stratified by baseline score, performed within each treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.
(b) Overall disease effect on ulcer rate from Cochran-Mantel-Haenszel test stratified by baseline score and treatment (p-value from Row Mean Scores Differ). Patients with 'Unknown' Endoscopy status were excluded.

Table 29 reveals the effect of aspirin on ulcer rates. Together with data from 021 this table would suggest that aspirin represents a significant risk factor for ulcers in the celecoxib group. This effect is not noted however in the other studies. The other studies that included naproxen (021 and 022) both showed a "protective effect" of low dose aspirin on the ulcer rates in the naproxen groups. The results in this study were not consistent. It is unclear if there is any real biologic phenomena accounting for the striking counter intuitive results in study 22 and to a lesser extent in study 021, or whether we are seeing multiple confounding factors or a statistical anomaly.. The issue will be addressed later in the review.

Table 29 (from study 062)

TABLE 15
GASTRODUODENAL ENDOSCOPY RESULTS
PART 8.1 OF 8: COMPARISON OF ASPIRIN USE
WITHIN EACH TREATMENT GROUP

INTENT-TO-TREAT COHORT (ITT)

		SC-58635 200MG BID (N= 269)	NAPROXEN 500MG BID (N= 267)	P-VALUE (b)
WEEK 0-4	CRUDE ULCER RATE BY STATUS			0.008
	USED ASPIRIN	13.5% (5/ 37)	29.0% (9/ 31)	
	DID NOT USE ASPIRIN	2.3% (5/215)	17.6% (38/216)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	<0.001	0.230	
WEEK 0-8	CRUDE ULCER RATE BY STATUS			0.016
	USED ASPIRIN	21.2% (7/ 33)	40.0% (12/ 30)	
	DID NOT USE ASPIRIN	3.9% (8/204)	30.7% (61/199)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	<0.001	0.536	
WEEK 0-12	CRUDE ULCER RATE BY STATUS			0.156
	USED ASPIRIN	24.1% (7/ 29)	42.9% (12/ 28)	
	DID NOT USE ASPIRIN	6.0% (11/182)	40.3% (75/186)	
	P-VALUE FOR WITHIN TREATMENT DIFFERENCE (a)	<0.001	0.726	

(a) Cochran-Mantel-Haenszel test stratified by baseline, performed within each treatment (from Row Mean Score Differ.)
(b) Overall subgroup effect on ulcer rate from CMH test stratified by baseline and treatment (from Row Mean Score Differ.)

Analysis of risk factors reveals a trend towards a more significant impact of age, ulcer bleeding and a history of cardiovascular disease in the celecoxib group compared to the naproxen group. The associated risk of NSAID intolerance and history of gastroduodenal ulcer affected both groups similarly. Steroid and DMARD use showed no significant impact on ulcer incidence in either group.

v. Summary:

Study 062 reveals a statistically significant lower ulcer rate in celecoxib treated patients compared to naproxen during all intervals studied. Similar to the pattern in study 071, the highest ulcer rates were seen in the first 4-week interval. Clinically significant endpoints of GI bleeding and gastric outlet obstruction occurred in 2 patients on the naproxen groupand no patients in the celecoxib group. As noted, celecoxib was associated with a higher ulcer rate that historical data on untreated patients and placebo groups elsewhere in this submission.

F. Study 041: A six month double-blind, randomized, parallel group study to compare celecoxib 200mg b.i.d. and diclofenac SR75 mg b.i.d. for antiarthritic efficacy,